# IMAGING OF INFECTION: A CORRELATIVE AND ALGORITHMIC APPROACH

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لازال اكتشاف وتحديد مكان الخمج بالتصوير الإشعاعي يشكل نقطة نقاش دائم بين الأطباء السريرين وأخصائي التصوير الإشعاعي. مع التقدم المطرد في مجال البحوث والتقنية ، هناك المزيد في قائمة الطرز المستخدمة حاليا أو تطوير تقنية صيدلانية وإشعاعية لتصوير أماكن الخمج.
ونظرا لعدم ملائمة طراز واحد لجميع المتطلبات، فيجب تطويع استراتيجية التصوير الإشعاعي لتشخيص الخمج في الأنسجة الرخوة والأنسجة العظمية لكل مريض على حده حسب معطيات حالته السريرية وتاريخه المرضي لحالته الحالية والسابقة، وتحديد المكان المحتمل للخمج طبقا لهذه المعطيات. وقد يتحقق ذلك بالاستخدام الأمثل وذو الكلفة المعقولة لطرز التصوير الأشعاعي المختلفة
**الكلمات المرجعية**: الخمج، التصوير الإشعاعي،ٔخراج، إلتهاب العظامٌ

*Detection and localization of infection can still be a dilemma for both clinicians and imaging specialists. The list of morphologic and physiologic modalities is increasing with the advancement of research, expanding the applications of existing modalities and developing new radiopharmaceuticals for infection imaging.*
*Since no single modality is appropriate for all situations, imaging strategy for the diagnosis of infection in both soft tissue and bone should be tailored for individual patients according to the detailed clinical data including the history of underlying and previous disease processes and the site of suspected infection for proper and cost effective utilization of the different imaging modalities.*

*Key Words: Infection, Imaging, Abscess, Osteomyelitis*

## INTRODUCTION

Inflammation was described on an Egyptian papyrus as early as 3000 BC.[1] Today it is still a common problem despite the advancement in prevention and treatment methods. The delineation of the extent and site of inflammation is crucial in the clinical management of infection and in monitoring the response to therapy.[2]

Many morphologic and functional imaging modalities are available to help accomplish this task. However, none of them is ideal in all situations. The choice depends on several factors including the site of poss ible infection, whether normal anatomy is presented or altered by surgery or trauma, duration of symptoms and signs, and other underlying diseases such as cancer or other causes of immune suppression.

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In general, early detection and treatment of focal infections is crucial as the mortality could be high particularly in abdominal abscesses.[3]

## PATHOPHYSIOLOGY

Inflammation is a complex tissue reaction to injury. Injury may be caused by microbes leading to infection, and by chemical, physical, immunologic or radiation injurious agents. Inflammation is fundamentally a protective reaction against the cause of cell injury as well as the consequences of such injury. However, inflammation may be potentially harmful and could be life threatening.[1,4]

Inflammation is classified predominantly into acute and chronic. Acute inflammation is the immediate and early response to injury that has relatively short duration lasting for minutes, hours or few days. Its main characteristics are vasodilatation following transient vasoconstriction, increased permeability with extravasation of protein rich fluid into the extra-vascular spaces (exudate) exudation of fluid and proteins and immigration of leukocytes predominantly neutrophils into the extra-vascular space. Chronic inflammation, on the other hand, is characterized by a proliferative (fibroblastic) rather than an exudative response with predominantly mononuclear cell infiltration (macrophages, lymphocytes and plasma cells). Vascular permeability is also abnormal. Chronic inflammation is of longer duration, and may last weeks to years.[5]

## DIAGNOSIS AND LOCALIZATION OF INFECTION

Diagnosis and localization of infection by clinical and laboratory method may be difficult since the signs and symptoms and laboratory data are non-specific. Accurate and rapid localization of infection facilitates rapid implementation of a tailored therapeutic regimen to decrease the mortality and complications.

Several diagnostic imaging procedures of two complimentary types are used, morphologic and functional imaging modalities. Morphologic modalities such as standard radiographs, ultrasonography (US), computerized tomography (CT) and magnetic resonance imaging (MRI) depends mainly on structural changes, variations in density and differences in proton content in tissues.

Functional modalities or nuclear medicine procedures depend on the physiologic changes. These modalities are numerous which indicates that no single modality is ideal in all situations and imaging should be tailored on individual basis. Many radioisotopes have been used to detect and localize infection (Table 1). Indium-111 leukocyte imaging accuracy was found to be best for relatively acute infections (less than 2 weeks) with 27% false negatives among patients with prolonged infections. On the other hand, gallium-67 imaging had its highest sensitivity in long standing processes with false negative results of 19% in relatively acute infections of less than one week duration.[6] Bitar, et al[7] in a comparative study in rabbits with experimental abscesses found that Indium-111 leukocytes were clearly superior to gallium for imaging early abscesses. Accordingly, labeled leukocytes available are more suitable for acute infections of short duration while Ga-67 is better in infections of longer duration.

Human non-specific polyclonal immunoglobulin (IgG) has been used for infection imaging.[2] Gamma camera images demonstrated successfully various foci of infection.[2,6] It was found to be more sensitive and

specific than Ga-67 for infection and to be superior to antigranulocyte antibodies and is as useful as labeled leukocytes in diagnosing infections. Serial In-111 IgG scans were also found to be useful for monitoring therapy and providing proof of cure.[8]

***Table 1**: Radiopharmaceuticals for infection*[11,62-64]

| | |
|---|---|
| 1. | Gallium-67 citrate |
| 2. | Labeled white blood cells using In-111 oxine or Tc-99m HMPAO (Tc-99m hexamethyl propyleneamine oxime |
| 3. | Labeled large protein |
| | 3.1. Nonspecific immunoglobulins |
| | 3.2. Specific immunoglobulins: polyclonal and monoclonal |
| | 3.2.1. Antigranulocyte monoclonal antibodies |
| | 3.2.2. Anti E-selectin antibodies |
| 4. | Labeled particles |
| | 4.1. Nonocolloid |
| | 4.2. Liposomes |
| 5. | Labeled receptor-specific small proteins and peptides |
| | 5.1. Chemotactic peptides |
| | 5.2. Interleukins |
| 6. | Labeled antibiotics: ciprofloxacin |
| 7. | F-18 FDG |

Recently In-111 and Tc-99m labeled chemotactic peptide analogs are useful for detecting and localizing infections. These agents have a potentially important advantage over the use of other isotope agents as imaging can be performed in less than three hours post infection compared to 18-24 hours or more for most other agents.[9-11]

Labeled liposomes have been used for scintigraphic imaging of infection[12] and inflammation.[13] Boerman, et a1[14] showed that the uptake in rat abscess was twice as high as that of IgG and the abscess could be visualized as early as 1 hour post injection. Positron Emission Tomography (PET) has recently been also used for detecting infections and shows promise.[15,16] However, it is not widely available.

The focus in the rest of this review will be on the main radiopharmaceuticals available in addition to the morphologic modalities in the diagnosis of soft tissue and skeletal infection.

## IMAGING OF SOFT TISSUE INFECTIONS

The imaging stategy of soft tissue infections depends on whether localizing signs and symptoms are present, and the location and duration of suspected infection.

### 1. Localizing signs present

#### *A. Abdominal infection*

If localizing signs suggest abdominal infection,, morphologic modalities, US, CT or MRI may be used first depending on the location of suspected infection. Standard radiographs have low sensitivity although findings when seen are specific.

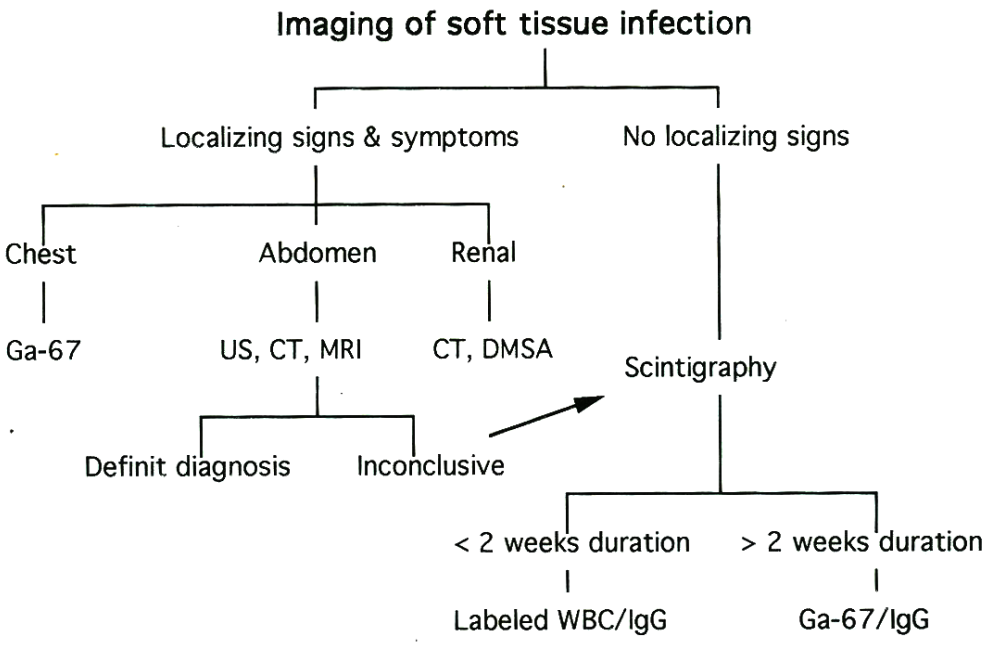
The advantages of these modalities are numerous but most importantly they provide quick results and adequate anatomic details and can guide needle aspiration to drain abscesses. US also has the advantage of being portable and so convenient for use for

critically ill patients. One of the major limitation of these modalities is the inability to differentiate infected from non-infected tissue abnormalities particularly in the early stages of infection (phlegmon) before the formation of abscesses.

Nuclear Medicine modalities are used for abdominal infection for confirmation of infection if the results of the morphologic modalities are inconclusive and in inflammatory bowel syndrome where labeled WBC have a major role in evaluating the disease activity.[17,18] These modalities may be preferred for use initially in cancer patients particularly those with surgical interventions. The major advantage of Nuclear Medicine modalities is the ability to image the entire body, hence they are particularly recommended for patients with no localizing signs. Labeled WBC studies are the most specific for acute infections.[19] Tc-99m HMPAO labeled WBC can also be used in critically ill patients,[20] since it can provide quicker results in comparison to other conventional Nuclear Medicine studies such as Ga-67 or In-111 labeled WBC. Minoja, et al[21] reported a sensitivity of 95%, specificity of 91% and accuracy of 94% for Tc-99m labeled WBC scanning in Intensive Care Unit (ICU) patients with occult infection.

Figure 1 represents an algorithm for abdominal abscess imaging which helps to choose the suitable modalities depending on the clinical situation and understanding of the pathophysiologic basis of different modalties.

**Figure 1**




*Labeled WBC may be used but if negative, Ga-67 or labeled antibodies should follow before excluding chronic infection.

### *B. Chest Infections*

The chest is a common site of various types of infections, acute and chronic. It is common in the elderly and immunosuppressed patients including cancer patients. Although CT has been used to help detect chest pathology including infections, gallium-67 has been most commonly used for chest infection. In-111 leukocytes has limited utility.

Siemon, et al[22] studied Ga-67 imaging in a variety of pulmonary disorders in hundreds of patients with excellent sensitivity and specificity. Gallium-67 has also been widely used in AIDS patients to detect pneumocystis carinii pneumonia (PCP). It is highly sensitive and correlates with the response to therapy.[23] Ga-67 is also valuable in idiopathic pulmonary fibrosis, sarcoidosis and amiodarone toxicity.[24,25]

### *C. Renal Infections*

Despite the major advances in laboratory and imaging techniques and the dramatic improvement of antibiotic therapy, the incidence of end-stage renal disease has not significantly changed over the last few decades.[26] Since infection contributes to the incidence of end-stage renal disease, early diagnosis and prevention of infection is crucial. Renal infection is not uncommon in cancer patients including those with prostatic carcinoma. CT scan has good sensitivity and specificity in the diagnosis of renal infections.[26] IVP has very limited value when the question is urinary tract infection. It has sensitivity of only 25%.[27] Ultrasound has been used frequently to evaluate the kidneys with suspected infections. The sensitivity of US has been shown to be 40-50%[28,29] which is nearly half of that of cortical scintigraphy which has a sensitivity of 86%, using Tc-99m Glucaheptonate. Cortical scintigraphy should therefore be the modality of choice for detecting and following pyelonephritis.

### 2. No localizing signs present

In this case, which is a common occurrence particularly among cancer and immunosuppressed patients, Nuclear Medicine procedures are most suitable to be used first as they have the advantage of being able to screen the entire body.

The choice of radiotracer again depends on the availability and duration of infection (Figure 1). Indium labeled white blood cells, if available, are the most specific for acute infections although false positive results have been reported in some tumors, swallowed infected sputum, GI bleeding and sterile inflammation. False negative results have been reported in infections of more than one week particularly after 2 weeks duration.[5] Gallium-67 has been used for many years but it is less specific than labeled WBC as it is taken up by many tumors, and sterile inflammation. Labeled antibodies and peptides are also used and have a good potential for a specific diagnosis of infection.[9-11]

Correlation with morphologic modalities after localization of infection can be of great help in the diagnosis particularly after Ga-67 or labeled white blood cell imaging and in providing anatomic information before intervention (Figure 1).

## IMAGING OF SKELETAL INFECTION

Skeletal infections are still common in clinical practice in both children and adults. Detecting early infection when complete resolution is possible and limiting complications is crucial. Again, the clinical picture may be confusing and the laboratory findings are not specific.[30] Several imaging modalities are being utilized for detection of osteomyelitis. The choice of modality depends on clinical presentation, particularly its duration, whether the site of suspected infection has been affected by previous pathology, and site of suspected infection.[30]

**Acute Osteomyelitis**

Acute osteomyelitis may be hemogenous or non-hemogenous. Acute hemogenous osteomyelitis occurs more commonly in children and has a predilection for metaphyses of long bones, where blood is rich and relatively sluggish, which represents a good medium for bacterial lodgment and proliferation.[31,32]

Standard radiographs are not sensitive for early detection of ostomyelitis as the changes are only evident after 10 to 21 days from the time of infection.[33,34]

Bone scintigraphy using Tc-99m Methylene Diphosphonate (Tc-99m MDP) is very sensitive in the early diagnosis of osteomyelitis and can show the abnormality as early as 24 hours after infection.[35] When the bone has not been previously affected by other pathologic conditions (non-violated), the bone scan has high accuracy and is a cost effective modality for diagnosis of osteomyelitis with sensitivity and specificity of approximately 90%.[30]

If bone has been affected by a previous pathology (violated) particularly after orthopedic surgical procedures, the bone scan will still be highly sensitive but the average specificity is only approximately 34%.[30]

In such situations, unless the bone scan is unequivocally negative, an additional modality should be used, particularly scanning with leukocyte labeled with In-111 oxine or Tc-99m hexamethyl propylene amine oxime (HMPAO). Overall In-111 leukocyte studies have a sensitivity of approximately 88% and specificity of 84% for osteomyelitis.[30] This modality is particularly useful in excluding infection in previously violated bone sites such as postsurgical and posttraumatic conditions. Tc-99m HMPAO labeled leukocytes have similar sensitivity and specificity to those labeled with In-111 and can be used particularly in peripheral locations such as extremities.

Johnson et al[36] also found that the combination of bone scan and In-111 leukocyte scan had the highest diagnostic values (100% sensitivity, 80% specificity and 91% accuracy) in diabetic foot infection in comparison to bone scan or Ga-67 scan alone which were both of limited value. Grerand et al[37] found that the dual isotope scans have a sensitivity of 93% and specificity of 83% and can reliably determine the site and extent of osteomyelitis in the neuropathic diabetic foot. Single Photon Emission Computed Tomography (SPECT) studies using dual isotope methods[38] showed 85% sensitivity, 100% specificity compared to 85% sensitivity and 57% specificity for planar imaging of diabetic foot osteomyelitis. Simultaneous imaging with Tc-99m MDP and In-111 labeled WBC were used at 4 and 24 hours and were found helpful in certain cases with violated bone, particularly in diabetic foot. It was found that in our experience a comparison of the uptake of In-111 WBC at 4 and 24 hours was helpful in differentiating active osteomyelitis from other conditions particularly neuroarthropathy (unpublished data).

Since labeled leukocyte scans show uptake by active bone marrow, it may be difficult to differentiate this normal uptake from abnormal uptake as a result of infection particularly after surgical procedures that may alter the bone marrow distribution significantly.[39] Bone marrow scans using Tc-99m sulfur colloid or nano-colloid may be added and have been demonstrated to improve the specificity of such studies, as shown by Seabold, et al[39] and Palestro, et al.[40]

Labeled antibodies have also been used in recent years for the diagnosis of osteomyelitis. In-111 or Tc-99m labeled human non-specific polyclonal antibodies (IgG) are used more commonly than monoclonal anti-

bodies such as labeled antigranulocyte antibodies. IgG is available and is easier to prepare and use than labeled leukocytes. The results of IgG with a sensitivity of 95% and specificity of 83% are encouraging.[41]

MRI has a role in the diagnosis of osteomyelitis, and overall it has a sensitivity of 60-100% and a specificity of 50-95%.[42,43] Although the average overall accuracy of MRI is similar to that of multi-phase bone scans, it is not used routinely because of its high cost. Also in patients with violated bone, it has been reported that it was difficult to differentiate those with and without infection by means of MRI.[44] However, it is used on an individual basis in suspected vertebral osteomyelitis, complicated cases of chronic osteomyelitis and in situations where anatomic details are necessary for planning surgical intervention.[45]

Ultrasound is of help in cases of suspected inflammatory arthritis while CT scan is useful in detecting sequestra.

**Chronic Osteomyelitis**

This is a frequent complication of acute osteomyelitis. It is important to confirm or exclude the presence of chronic active infection since the continuation of intravenous antibiotic therapy and/or surgical intervention to eradicate infection will depend on that. The radiologic diagnosis of chronic active osteomyelitis is neither sensitive nor specific.[46] Bone scintigraphy is very sensitive but not specific.[47,48] This is the result of chronic bone repair with increased bone metabolism and increased uptake on bone scans in the absence of active infection. Bone scans may also remain abnormal for months even after the successful treatment of acute osteomyelitis. Therefore, it is difficult to differentiate healing from chronic active disease, although increased activity in all phases of a bone scan is more suggestive of chronic active disease. The bone scans accordingly will not confirm the presence of active disease but an unequivocally negative scan will exclude it. MRI has been found to have relatively higher specificity than the Tc-99m bone scan in chronic osteomyelitis.[49]

Gallium-67 citrate is also more specific than bone scanning for chronic osteomyelitis but false positives still occur in conditions such as healing fractures, non-infected prosthesis and tumors. Combined Tc-99m MDP and gallium-67 scans can be helpful in making a diagnosis of active disease. Tumeh, et al[47] suggested that this diagnosis can be made when gallium uptake exceeds Tc-99m uptake in intensity and/or spatial distribution. The role of leukocyte scanning in the diagnosis of chronic osteomyelitis is controversial since it may be a false negative in the presence of chronic active osteomyelitis.[50] CT scan has a role in the detection of sequestra in chronic osteomyelitis,[51] since determining the presence or absence of the sequestra is important for taking decisions with regard to surgical intervention. MRI was also found to be useful in detecting sequestra and in identifying the presence and sites of chronic active infection.[42]

Tc-99m polyclonal IgG and Tc-99m monoclonal antigranulocyte antibodies also have been used in chronic osteomyelitis.[52] However, more experience is needed to evaluate further the accuracy of these agents in detecting osteomyelitis.

**Specific forms of skeletal infections**

Vertebral osteomyelitis has been seen more often in recent years. It occurs more frequently in the lumbar region followed by thoracic and cervical spine. It occurs most frequently in adults with a mean age of 60-70 years, usually resulting from haematogenous spread of organism to the bone. Other causes include extension of infection from adjacent structures and complications from

spine surgery and trauma. Predisposing factors include cancer, urinary tract infections, urinary tract instrumentation (which may be used in cancer patients) and diabetes mellitus.[6] Signs and symptoms of vertebral osteomyelitis are usually vague and the diagnosis may be delayed. Accordingly, this form of skeletal infection is considered one of the chronic forms of osteomyelitis. Standard radiographs are neither sensitive nor specific.[46,53-55] Bone scan may be sensitive but is not specific, since the spine is a common site for many pathologies including spondylitis and metastases. In addition, in some cases of proven osteomyelitis, bone scans have been negative as late as two weeks following the onset of symptoms.[55] Increased uptake of Tc-99 MDP also does not differentiate between active and inactive osteomyelitis because the uptake of previous disease may persist for a long time.[56] In-111 leukocyte scanning has also shown a lack of sensitivity for vertebral osteomyelitis. The sensitivity of In-111 labeled leukocytes for vertebral osteomyelitis is only approximately 30%.[43,54,57,58] This low sensitivity is due to different patterns of uptake in cases of proven vertebral osteomyelitis including normal uptake, decreased uptake or increased uptake.[57] The specificity of increased uptake pattern of labeled white blood cells, however, is approximately 98%.[54,57]

Gallium-67 has a sensitivity of 88% and a specificity of 100% when combined with Tc-99m MDP. MRI is also sensitive (98%) and specific (93%) for vertebral osteomyelitis.[42] MRI has the advantage of providing clear anatomic details for possible surgical intervention.

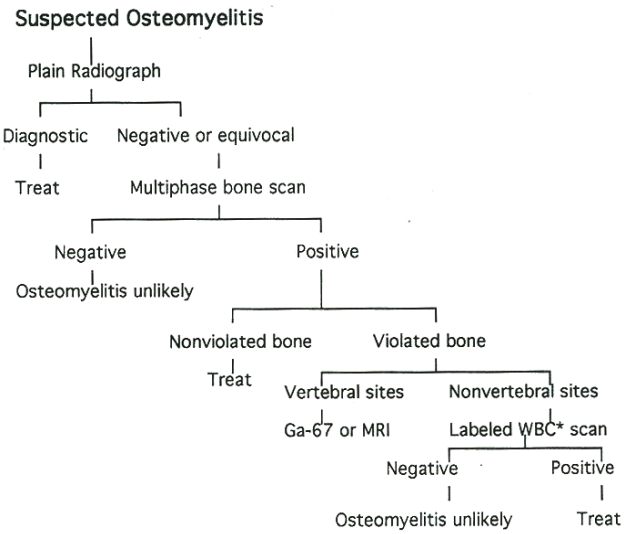
Diagnosis of infection after prostheses which are not uncommonly performed in cancer patients, is a difficult task. The bone scan again is not specific. In-111 leukocyte scan may show false positive results because of considerable variation in marrow distribution secondary to surgery, which also has been reported after radiation therapy and trauma.[39] Focal and diffuse uptake of In-111 leukocytes around a prosthesis was found up to two years in 48% of uncomplicated cases.[59] Although Oswald, et al[60] found that this uptake decreased with time, a single study cannot differentiate uptake secondary to infection from that resulting from physiologic bone marrow uptake. Addition of Tc-99m sufur colloid or nanocolloid bone marrow scanning to In-111 leukocyte scanning improved the specificity and is currently the recommended modality for evaluating periprosthetic infection as well as in patients with fracture.[39,40,61] The study is considered positive for infection when the localization of In-111 leukocytes corresponding to the site of bone scan uptake exceeds Tc-99m colloid on bone marrow scan in extent and or focal intensity (discordant). If the intensity and distribution of In-111 labeled leukocytes localization is equal, to that of Tc-99m colloid (concordant pattern) the studies are considered negative for infection.

Figure 2 summarizes a general outline that can be followed to tailor the plan of imaging of suspected skeletal infection particularly when bone is violated by possible tumor, fracture or surgical intervention.

**Assessing the response to therapy**

Several nuclear medicine studies are generally useful to achieve the evaluation of the response to therapy. Bone scan is not a suitable modality to determine the response to therapy of skeletal infections because it may remain positive for years in the absence of active infection. Gallium-67, labeled white blood cell or radio-labeled antibody serial studies are useful in determining the response to therapy of infection of both soft tissue and bones.

Figure 2




* Ga-67 may be used instead if chronic infection is suspected or if WBC scan is not available .

**REFERENCES**


1. Weissman G. Inflammation . Historical perspectives. In Gallin JI, et al (Eds): Inflammation : Basic principles and clinical correlates, 2nd ed. New York, Raven Press;1990. 5-13.
2. Rubin RH, Fischman AJ, Callahan RJ, Khan BA, Keech F, Ahmad M, et al. In-111 labeled non specific immuno-globulin scanning in the detection of focal infection. NEJM 1989; 321:935-40.
3. Freifeld AG, Pizzo PA, Walsh TJ. Infections in the cancer patient. In : Principles and Practice of Oncology, 5th edition. (Devita VT, Hellman S, Rosenberg SA, Eds) Philadelphia: Lippincott Raven;1997, 2659-704.
4. Woods G, Gutierrez Y, Walker D, Purtilo D, Shanley J. Diagnostic pathology of infectious diseases. Philadelphia, Lea & Febiger, 1993.
5. Sfakianakis GN, Al-Sheikh W, Heal A, Rodman G, Zeppa R, Serafini A. Comparison of scintigraphy with In-111 leukocytes and Ga-67 in the diagnosis of occult sepsis. J Nucl Med 1982;23: 618-26.
6. Cotran RS, Kumar V, Robins SL editors. Inflammation and repair in Robbins pathologic basis of disease. 5th edition. Philadelphia; Saunders;1994. 51-92.
7. Bitar RA, Scheffel U, Murphy PA, Bartlett JG. Accumulation of In -111 labeled neutrophils and gallium-67 citrate in rabbit abscesses. J Nucl Med 1986;27: 1883-9.
8. Rubin RH, Fishman AJ. The use of radiolabeled non specific immunoglobulin in the detection of focal inflammation. Semin Nucl Med 1994;24:169-79.
9. Van der Laken CJ, Boerman OC, Oyen WJG, van den Ven MTP, Edwards DS, Barrett JA, van der Meer JWM, Corsten FHM. Technetium-99m labeled chemotactic peptides in acute infection and sterile inflammation. J Nucl Med 1997;38: 1310-5.
10. Babich JW, Tompkins RG, Graham W, Barrow SA, Fischman AJ. Localization of radiolabeled chemotactic peptide at focal sites of Escherichia Coli infection in rabbits: Evidence for a receptor specific mechanism. J Nucl Med 1997;38: 1316-22.
11. Vallabhajosula S. Tc-99m labeled chemotactic peptides: specific for imaging infection. JNM 1997; 38: 1322-6.
12. Morgan JR, Williams LA, Howard CB. Technetium labeled liposome imaging for deep seated infection. Br J Radiol 1985; 58: 35-9.
13. O'Sullivan MM, Powell N, French AP, Williams KE, Morgan JR, Williams BD. Inflammatory joint disease: a comparison of liposome scanning, bone scanning and radiography. Ann Rheum Dis 1988; 47: 485-91.
14. Boerman OC, Storm G, Oyen WJG, van Bloois L, van der Meer JWM. Sterically stabilized liposmes labeled with In-111 to image focal infection. J Nucl Med 1995; 36: 1639-44.
15. Ichiya Y, Kuwabara Y, Sasaki M, Yoshida T, Akashi Y, Murayama S, et al. FDG-PET in infectious lesions: The detecton and assessment of lesion activity. Annals of Nuclear Medicine 1996;10: 185-91.

16. Bakheet S, Powe J. Benign causes of FDG-18 uptake on whole body PET scans. Seminars of nucl Med (In press).
17. Gibson P, Lichtenstein M, Salahi N, Hebbard G, Andrews J. Value of positive technetium-99m leucocyte scans in predicting intestinal inflammation. Gut 1991; 32: 1502-7.
18. Scholmerich J, Schmidt E, Schumichen C, Billmann P. Scintigraphic assessment of bowel involvement and disease activity in Crohn's disease using Technetium-99m Hexamethyl Propylene Amine Oxine as leukocyte label. Gastroenterology 1988;195:1287-93.
19. Datz FL. Abdominal abscess detection : Gallium, In-111 and Tc-99m labeled leukocytes and polyclonal and monoclonal antibodies. Semin in Nucl Med 1996; 26: 51-64.
20. Kao CH, Wang JL, Liao SQ, Wang SJ. Tc-99m HMPAO labeled WBC's in the detection of occult sepsis in the intensive care unit. Intensive Care Medicine 1992; 18: 15-9.
21. Minoja G, Chiaranda M, Fachinetti A, Raso M, Dominioni L, Torre D, De Palma D. The clinical use of Tc-99m labeled WBC scintigraphy in cliniclaly ill surgical and trauma patients with occult sepsis. Intensive Care Medicine 1996; 22: 867-71.
22. Siemon JK, Siegfried GF, Waxman AD. The use of Ga-67 in pulmonary disorders. Sem Nucl Med 1978;3: 235-49.
23. Woolfenden JM, Corrasquillo JA, Larson SA, Simmons TJ, Masur H, Smith PD, et al. Acquired immunodeficiency syndrome: Ga-67 citrate imaging. Radiology 1987;162: 383-7.
24. Moinuddin M, Rackett J. Gallium scintigraphy in the detection of amiodarone lung toxicity. AM J Radiology 1986;147 : 607-9.
25. Coak PS, Datz FL, Disbro MA, Alazaraki N, Taylor A . Pulmonary uptake in Indium-111 leukocyte imaging: clinical significance in patients with suspected occult infections. Radiology 1984;150:557-61.
26. Papanicolaou N, Pfister RC. Acute renal infections. Radiol Clin North Amer 1996; 34: 965-95.
27. Little PJ, McPherson DR, De Wardener HE. The appearance of the intravenous pyelogram during and after acute pyelonephritis. Lancet 1965;1:1186-8.
28. Conway JJ. Role of scintigraphy in urinary tract infection. Seminars in Nuclear Medicine 1988; 18: 308-19.
29. Mackenzie JR. A review of renal scarring in children. Nucl Med Comm 1996;17: 176-90.
30. Elgazzar AH, Abdel-Dayem HM, Clark JD, Maxon HR. Multimodality imaging of osteomyelitis. Eur J Nucl Med 1996;22: 1043-63.
31. Nixon GW. Acute hematogenous osteomyelitis. Pediatr Anal 1976; 5: 64-81.
32. Trueta J. The three types of acute hematogenous osteomyelitis: a clinical and vascular study. J Bone Joint Surg Br 1959; 41: 671-80.
33. Waldvogel FA, Medoff G. Swartz MN. Osteomyelitis: a review of clinical features, therapeutic considerations and unusual aspects (part I) N Engl J Med 1970; 282: 198-206.
34. Bonakdar-pour A, Gaines VD. The radiology of osteomyelitis. Orthop Clin North Am 1983; 14: 21-37.
35. Handmaker H. Leonards R. The bone scan in inflammatory osseous disease. Semin Nucl Med 1976; 6: 95-105.
36. Johnson JE, Kennedy EJ, Shereff MJ, Patel NC, Collier BD. Prospective study of bone, In-111 labeled white blood cell and gallium scanning for the evaluation of osteomyelitis in the diabetic foot. Foot Ankle Int 1996; 17: 10-6.
37. Grerand S, Dolan M, Laing P, Bird M, Smith ML, Klenerman L. Diagnosis of osteomyelitis in neuropathic foot ulcers. J Bone Joint Surg (Br) 1996; 78(B): 51-5.
38. Ezuddin S, Yuille D, Spiegelhoff D. The role of dual bone and WBC scan imaging in the evaluation of osteomyelitis and cellulitis using both planar and SPECT imaging. J Nucl Med 1992; 33:839.
39. Seabold JE. Nepola JV, Marsh JL, Hawes DR, Justin EP, Ponto JA et al . Post operative bone marrow alterations: potential pitfalls in the diagnosis of osteomyelitis with In- 111 -labeled leukocyte scintigraphy. Radiology 1991; 180: 741-7
40. Palestro CJ, Swyer AI, Kim CK, Goldsmith SJ. Infected knee prosthesis: diagnosis with In-l l l leukocyte, Tc-99m sulfur colloid and Tc-99m MDP imaging. Radiology 1991; 179: 645-8.
41. Bihl H, Rossler B, Borr U. Assessment of infectious conditions in the musculoskeletal system: Experience with Tc-99m HIG in 120 patients. J Nucl Med 1992; 33: 839.
42. Mason MD, Zlatkin MB, Esterhai IL, DaLinka MK, Velchik MG, Kressel HY. Chronic complicated osteomyelitis of the lower extremity: evaluation with MR imaging. Radiology 1989; 173: 355-9.
43. Meyers P, Wiener S. Diagnosis of hematogenous pyogenic vertebral osteomyelitis by magnetic resonance imaging. Arch Intern Med 1991; 151: 683-7.
44. Berquist TH, Brown ML, Fitzgerald RH, May GR. Magnetic resonance imaging : Application in musculoskeletal infection. Mag Res Imaging 1985;3:219-30.
45. Kim CK, Kim SY, Alavi A, Esterhai J. Chronic osteomyelitis at the site of fracture or surgery in the lower extremity: In-l l l WBC vs MRI. J Nucl Med 1992; 33: 902.
46. Tumeh SS, Aliabadi P, Weissman BN, McNeil BJ. Disease activity in osteomyelitis: role of radiography. Radiology 1987; 165: 781- 4.
47. Tumeh SS, Aliabadi P. Weissman BN, McNeil BJ. Chronic osteomyelitis: bone and gallium scan patterns associated with active disease. Radiology 1986; 158: 685-8.

48. Schauwecker DS. Osteomyelitis: diagnosis with indium-111 labeled leukocytes. Radiology 1989; 171: 141-6.
49. Carstens MC, Erdman WA, Tamburro F. Walker, B, Bonte F. Osteomyelitis: comparison of MRI and radionuclide (RN) studies. J Nucl Med 1992; 33:992.
50 Tumeh SS, Tohmeh AG. Nuclear medicine techniques in septic arthritis and osteomyelitis. Rheum Dis Clin North Am 199l;17: 559-83.
51. Tumeh SS, Aliabadi P. Seltzer SE, Weissman BN, McNeil BJ. Chronic osteomyelitis: the relative role of plain radiographs and transmission computed tomography. Clin Nucl Med 1988; 13: 710.
52. Sciuk I, Brandau W. Vollet B, Stucker R, Erlemann, R, Bartestein P, et al. Comparison of technetium-99m polyclonalhuman immunoglobulin and technetium-99m monoclonal antibodies for imaging chronic osteomyelitis. Eur J Nucl Med 1991; 18: 401-7.
53. Schlaeffer F, Mikolich DJ, Mates SM. Technelium-99m diphosphonate bone scan: False-normal findings in elderly patients with hematogenous vertebral osteomyelitis. Arch Intern Med 1987; 147: 2024-6.
54. Modic MT, Feiglin DH, Piraino DW, Boumphrey F, Weinstein MA, Duchesneau PM, Rehm S. Vertebral osteomyelitis: assessment using MR. Radiology 1985(5) : 157-66
55. Abbey DM, Hosea SW. Diagnosis of vertebral osteomyelitis in a community hospital by using computed tomography. Arch Intern Med 1989; 149: 2029-35.
56 Kern RZ, Houpt TB. Pyogenic vertebral osteomyelitis: diagnosis and management. Can Med Assoc J 1984;130:1025-8.
57. Palestro Cl. Kim CK. Swyer AJ, Vallabhajosula S, Goldsmith SJ. Radionuclide diagnosis of vertebral osteomyelitis:indium-111-leukocyte and technetium-99m-methylene diphosphonate bone scintigraphy. J Nucl Med 1991;32:1861-5.
58. Fernandez-Ulloa M, Vasavada Pl, Hanslits MJ, Volarich DT, Elgazzar AH. Vertebral osteomyelitis imaging with In-l l l labeled white blood cells and Tc-99m bone scintigrams. Orthopedics 1985; 8: 1144-50.
59. Oswald SG, VanNostrand D, Savory CG, Callaghan JJ. Three phase bone scan and indium white blood cell scintigraphy following porous-coated hip arthroplasty: a prospective study of the prosthetic hip. J Nucl Med 1989;30:1321-31.
60. Oswald SG, VanNostrand D, Savory CG, Anderson JH, Callaghan JJ. The acetabulum: a prospective study of three-phase bone and indium white blood cell scintigraphy following porous coated hip arthroplasty. J Nucl Med 1990;31: 274-80.
61. Elgazzar AH, Young HW, Webner PJ. Indium-111 leukocyte and Tc-99m sulfur colloid uptake in Paget's disease. J Nucl Med 1995; 36: 858-61.
62. Chianelli M, Mather SJ, Martin-Comin J, Signore A. Radiopharmaceuticals for the study of inflammatory process. A review. Nucl Med Commun 1997;18: 437-55.
63. Datz FL, Morton KA. Radionuclide detection of occult infection: Current strategies. Cancer Invest. 1992; 9: 691-8.
64. Corstens FHM, van der Meer JWM. Chemotactic peptides: New locomation for imaging of infection. J Nucl Med 1991; 32: 491-4.