Chapter 9

Infectious Foci Imaging with Targeting Radiopharmaceuticals in Nuclear Medicine

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/52882

1. Introduction

Despite the advances in public health during the 18th and 19th centuries and the introduction of immunization and antibiotics in the 20th century, bacterial infection is among the most frequently encountered and costly causes of diseases and one of the major causes of morbidity and mortality especially in developing countries (El-Ghany et al., 2005). Localizing and distinguishing the "infection foci" in body sites are very important and life saving processes. The identification of an infection at early stage of disease is critical for a favorable outcome. The diagnosis of deep seated infections such as osteomyelitis, endocarditis and intra-abdominal abscesses is still a challenging problem. Although imaging techniques such as x-ray, computerized tomography (CT-scan), magnetic resonance imaging (MRI) and ultrasonography (US) might be helpful, but none of these techniques are specific for infection diagnosis because of their limitations due to insignificant anatomical changes in the early stages of the infection process. In addition, these techniques are not capable of differentiating between inflammatory and infectious processes. In contrast, nuclear medicine procedures can determine the location and the degree of disease activity in infectious processes based on physiologic and/or metabolic changes that are associated with these diseases rather than gross changes in the structure (Hall et al., 1998). This method requires a reliable radiopharmaceutical that can selectively concentrate in sites of infection. Various ^{99m}Tc-labeled compounds have been developed for the scintigraphic detection of infection and sterile inflammation in humans. Unfortunately, these radiopharmaceuticals do not discriminate between infection and sterile inflammatory process, which is often of clinical importance (Welling et al., 2001). In recent years, the development of radiolabeled antimicrobial agents for specific diagnosis of infection has received considerable attention, sparking a lively debate about the infection specificity of these radiopharmaceuticals (Oyen et al., 2005). Direct

targeting of the locally present microorganisms is a new approach for improving the selectivity of radiopharmaceuticals for infection detection in nuclear medicine (Kyprianidou et al., 2011). The use of radiolabeled antibiotics and antimicrobial peptides are fast emerging as promising targeted diagnostic tests for detection of infective lesions because of their specific binding to the bacterial component. These targeting molecules reliably locate sites of infection and make a differential diagnosis between infection and sterile inflammation. In this chapter, the new approaches to scintigraphic imaging of infection and inflammation by radiolabeled antibiotics and antimicrobial peptides are thoroughly discussed in order to assess their diagnostic value as targeting imaging radiopharmaceuticals.

2. Inflammation and infection

Inflammation and infection are different processes. Inflammation is merely a nonspecific immune response-one which does not require the presence of microorganisms to occur. Inflammation can occur from trauma, ischemia, neoplasm, autoimmune attack or invasion by microorganisms (Petruzzi et al., 2009). Infection can be considered as a special subcategory of inflammatory disease, i.e. an inflammatory reaction of the host in response to invasion by microorganisms (Oyen et al., 2005). All inflammatory processes develop along a known sequence: locally increased blood supply, leakage of a fluid, small molecules and proteins and infiltration of cells (Rennen et al., 2002). In response to tissue damage, powerful defense mechanisms are activated, consisting of leukocytes and plasma proteins. Furthermore, a complex of variety of chemical mediators is involved. The migration of leukocytes from the blood stream is facilitated by chemical mediators which up regulated the expression of adhesion molecules on endothelial cells and leukocytes. This process starts within minutes from the injury and resolves in hours or days. It causes the classical symptoms of acute inflammation; rubor (redness), calor (warmth), tumor (edema), dolor (pain) and fastio laesa (impaired function) (Bleeker-Rovers, 2004). The ability to identify focal sites of infection in patients who do not present with localizing symptoms is a key step in delivering appropriate medical treatment. This is particularly critical in immune compromised patients, since signs and symptoms of infection may be minimized in patients with neutropenia (Babich & Fischman, 1999). There are several reasons why imaging of infection and inflammation and distinguishing between them becomes increasingly important in the next decade. The population is ageing; the application of implants and transplants is increasing. The number of immune compromised patients is growing, mainly because of frequent use of chemotherapeutic agents leading to neutropenia. Furthermore, the increased use of antibiotics leads to insensitivity for some of these pharmaceuticals (Larverman et al., 2008).

3. Types of infection

The most common infections are: (1) *Pneumocystis carinii* pneumonia (PCP) which, the large number of patients receiving chemotherapy or harboring the HIV (human immunodeficien-

http://dx.doi.org/10.5772/52882

cy virus) are susceptible to opportunistic infection, (2) protozoal infections include crytosporidiosis and toxoplasmosis (abscess, encephalitis), (3) viral infections include cytomegalovirus (retinitis, adrenalitis, lung, neurological, disseminated) and herpes viruses (simplex and zoster), (4) fungal infections include *Cryptococcos neoformans* (meningitis, pneumonitis, disseminated) and (5) bacterial infections (specially *Stereptococcos* and *Haemophilus*) are being seen more frequently in children and intravenously drug users. Other bacterial infections include *Listera monocytogenes*, *Salmonella*, *Nocardia* and *Mycobacteria* both *toberclusis* and *avium* intracellular (Roohi, 2006).

Infections can also be classified according to the type of pathogens including: (1) opportunistic infections: infections caused by microbes belonging to the normal host flora and that initiate an infective process consequently to environmental changes, antimicrobial treatment, traumas and injuries, the reduction of the host immune defenses, or the migration to a new body-compartment, (2) exogenous infections: caused by pathogen organisms, which do not belong to the normal flora but are transmitted to healthy hosts from a contaminated environment (food and water) or from infected carriers (humans or animals). The main routes of transmission of exogenous pathogens from an infected carrier are the air and aerosol, sexual intercourse, blood transfusions or animal bites. Exogenous infections can be classified according to the site of acquirement in: (1) community-acquired infections: when the transmission occurs within the community, (2) healthcare-acquired infections: when the pathogen is transmitted within a hospital or a health-care institution; Finally, iatrogenic infections are those developed consequently to a medical procedure such as pharmaceutical treatment or surgery, and could be caused either by endogenous or exogenous pathogens (Baldoni, 2009).

4. Infection diagnosis techniques

The identification of infection at early stage of the disease is critical for a favorable outcome. Conventional methods of diagnosis, relying on examination and culture of organisms from infected foci have continued to advance embracing new technologies and automation. Despite this, these methods are still time consuming, insensitive and the results often obtain too late to guide clinical decision making (Wareham et al., 2005). Clinicians usually use a variety of laboratory tests, clinical and radiological tests, to aid diagnosis and make a decision (Yurt Lambrecht et al., 2008a).

4.1. Laboratory tests

Many current laboratory tests used to guide the diagnostic process rely on factors in the inflammatory response: erythrocyte sedimentation rate, white-blood cell count, acute-phase proteins and cytokines, but the tests are not specific enough to discriminate between infection and inflammation. New techniques, especially within immunology and molecular biology, are yielding new insights into the discrimination of infection and inflammation (Yurt Lambrecht et al., 2008b).

4.2. Imaging techniques

Imaging techniques can be classified as either structural or functional. Structural imaging procedures are used to evaluate macroscopic morphological changes and implant loosening. Differently, functional imaging procedures aim to visualize the specific accumulation of an injected gamma-emitter radiotracer at the site of infection (Baldoni, 2009). Structural imaging methods like x-ray, US, CT-scan and MRI are based on important anatomic alterations and the possibility of a precocious diagnosis is limited. These are not the best of methods for the localization of infection at early stages (Diniz et al., 2005). These procedures detect the morphologic alterations of the tissues after significant process has taken place in the infective site leading to abscess formation (Motaleb, 2007a). The results of these techniques are unsatisfactory in the early stages of the diseases (Shah & Khan, 2011a), while nuclear medicine images are functional and can therefore identify the infection at the early stages (Mora et al., 2010).

4.2.1. X-ray

X-ray provides a powerful tool in medicine for mapping internal structures of the human body. Relatively inexpensive and readily available, radiographs should routinely be the initial imaging procedure performed in all patients suspected of having musculoskeletal infection. But, the earliest radiographic changes of osteomyelitis are soft-tissue swelling and blurring of adjacent fat planes, which may take several days to become apparent after the onset of infection. Approximately 10 days after the onset of infection, radiographs may demonstrate lysis of medullary trabeculae, focal loss of cortex, and periosteal reaction The sensitivity of plain radiography ranges from 43% to 75%, and the specificity from 75% to 83%. Though helpful when positive, a negative study does not exclude osteomyelitis (Palestro et al., 2006). Despite its limitations, radiographs remain the best initial examination in cases of symptomatic postoperative patients and may depict findings associated with postoperative infection (Peterson, 2006).

4.2.2. Ultrasonography

Musculoskeletal tissues are, for the most part, accessible to examination by ultrasound, allowing its deployment as a first-line investigation in a wide range of musculoskeletal infections. In addition, ultrasound is noninvasive, portable, and versatile. Further, it does not use ionizing radiation, and it is relatively lower in cost. However, ultrasound images have a major disadvantage: poor quality because of multiplicative speckle noise that results in artifacts. Segmentation of lesions in ultrasound images is therefore a challenging task that remains an open problem despite many past research efforts (Yap et al., 2008). On the other hand, ultrasonography is very commonly used during the initial work-ups of children with urinary tract infection (UTI) because it gives a rapid anatomical overview of the kidneys, especially with regard to the dilatation of the collecting system (Wu et al., 2003). The disadvantages are that the results are highly operator-dependent, penetration and reflection of the sound waves in tissue may be hindered by gas (bowel) or dense structures (bone), and structures deep within the body may be difficult to visualize because the image quality suf-

http://dx.doi.org/10.5772/52882

fers from the longer wavelengths used for deep imaging (Gotthardt et al., 2010). UItrasonography is useful technique for diagnosing and localizing fluid collections, but it often cannot determine whether a particular fluid collection is infected or not (Fortner et al., 1986).

4.2.3. Computed Tomography (CT)

CT-scan is an x-ray imaging technique that produces three dimensions (3D) images of an object by using a series of two-dimensional (2D) set of images data to mathematically reconstruct a cross-section of it. CT is unique because it provides imaging of a combination of soft tissues, bone and vessels, and many studies have confirmed CT to be a valid complement to conventional imaging methods (Cotti & Campisi, 2004). CT is highly reproducible, has an excellent spatial resolution, and although more expensive than ultrasonography, is still relatively inexpensive. The disadvantages are exposure of the patient to radiation and lack of functional information (Gotthardt, 2010). It is also limited by a lack of specificity of many of the imaging findings that are noted in the setting of infection or inflammation (Kumar et al., 2008).

4.2.4. Magnetic Resonance Imaging (MRI)

While MRI provides very high resolution (up to 10 μm) and unlimited depth of penetration, it is, however, limited by low sensitivity, with detectabilities in the milli to micromolar (10^{-3} to 10^{-6}) range. Therefore, amplification techniques are often needed to image molecular processes *in vivo* (Bonekamp et al., 2010). Advantages of MRI are the superb anatomic details it reveals (including the ability to evaluate both bone and adjacent soft tissue), its lack of ionizing radiation, and its rapid completion. Disadvantages of MRI are occasional inability to distinguish infectious from reactive inflammation, and difficulty in imaging sites with metallic instrumentation such as joint prostheses (Palestro et al., 2006). It is also limited by a lack of specificity of many of the imaging findings that are noted in the setting of infection or inflammation (Kumar et al., 2008). Because of the long imaging times and the considerable exposure to noise, MRI is not convenient for patients. Furthermore, there are limitations to the scanning of patients with pacemakers, implants, and other devices, and the procedure is relatively expensive (Gotthardt et al., 2010).

5. Nuclear medicine

Nuclear medicine is a highly multi-disciplinary specialty that develops and uses instrumentation and radiopharmaceuticals to study physiological processes and non-invasively diagnose, treat and identifying the staging of a disease (Hricak, 2007). The radiopharmaceuticals are molecular and cellular structures labeled with a specific radionuclide and are applied to patients after appropriate quality control (Bernardo-Filho et al., 2008). A radiopharmaceutical is usually made up of two components: a basic substance for localization in a desired tissue or organ, and a radionuclide for tagging to the basic substance to emit the gamma rays that can be detected and imaged with a gamma camera. The efficacy of the radiopharmaceutical is therefore determined by these components (Korkmaz & Ozer., 2006). Radiophar-

maceuticals localize in inflamed or infected tissue in the body. The radiopharmaceuticals emit gamma rays that can be detected and imaged when a patient is placed in a gamma camera (Truluck, 2007). Radionuclide emission-based nuclear medicine modality is a noninvasive technique, which is a quick, sensitive, and specific method to detect as well as locate the lesion at any anatomical site at early stage of the disease (Singh & Bhatnagar, 2010).

5.1. Advantages of nuclear medicine technique

Nuclear medicine has an important role in adding the diagnosis of particularly deep seated infections such as abscesses, osteomylitis, septic arthritis, endocarditis and infections of prosthetic devices (Das et al., 2002). It provides information on pathophysiological and pathobiochemical processes. In this respect it differs from other current imaging procedures such as x-ray, CT and MRI, which supply information with high resolution on the morphological changes that occur in a specific disease. In addition, nuclear medicine technique permits whole-body imaging, whereas CT and MRI routinely focus on just a part of the body (Becker & Meller, 2001). Nuclear medical imaging has an important role in discriminating infections from inflammation. Inflammatory processes can be visualized in their early phases, when anatomical changes are not yet apparent (Yurt Lambrecht et al., 2008a). The early detection of the infectious focus by radionuclide imaging helps both patient and physician to reduce the cost and the length of hospitalization (El-Ghany et al., 2005).

5.2. Current radionuclides for infection imaging

The radionuclide is a substance which continuously emits the radiation. Generally this radiation consists of alpha-rays, beta-rays and gamma-rays (Patei Riddhi et al., 2011). Radiopharmaceuticals can be labeled with various radionuclides such as ^{67}Ga, ^{99m}Tc, ^{111}In, ^{18}F, ^{131}I, etc. (Oyen et al., 2001). Technetium-99m is one of the most desirable radionuclides that is used in clinical nuclear medicine, due to the emission of gamma ray of optimal energy (140 keV), a suitable half-life (6 h), availability from ^{99}Mo-^{99m}Tc generator systems and low cost (Arano, 2002, & Oyen et al., 2001).

5.3. Imaging systems in nuclear medicine for infection diagnosis

Gamma camera, single photon emission tomography (SPECT) and positron emission tomography (PET) are current imaging systems in nuclear medicine for infection diagnosis.

5.3.1. Gamma camera

In nuclear medicine, the most common imaging systems are general-purpose systems, which allow a wide variety of morphological and physiological studies. While dedicated x-ray equipments for specific examinations are largely found in diagnostic radiology, this is not the case for nuclear medicine, where general purpose gamma cameras are commonly used (Sanchez et al., 2004). Tools like portable gamma cameras make it possible to quickly and simply perform the gamma mapping of an area to be processed, with the advantage of remote measurements of hot spots, not necessarily on contact. However, the use of such

cameras on site sometimes comes up against an insufficient sensitivity or space resolution, or against their excessive bulk (Gal et al., 2006).

5.3.2. Single photon emission tomography

Single photon emission computed tomography (SPECT) is a functional and molecular imaging modality, which is being used clinically to localize targets prior to biopsy and surgery (Roper et al., 2012). SPECT shows function by means of a three dimensional activity distribution of a radioactive tracer, which was injected prior to the measurement (Changizi et al., 2008). The principal values of SPECT are, as the result of the disposability of numerous single-photon radiopharmaceuticals, its broad clinical availability and its versatility for the everyday management of patients affected by several different conditions. Moreover, it is able to increase contrast and to allow better delineation of pathologies than planar imaging. However, the main limitation of SPECT imaging is its poor anatomical information; in fact, it yields essentially functional or molecular information that therefore are very suitable to be integrated with imaging modalities such as CT or magnetic resonance imaging (MRI), which provide morphological details (Schillaci et al., 2007). The hybrid SPECT/CT system delivers the high sensitivity of scinitigraphic technology with the high specificity of CT. This reduces the disadvantage of the SPECT's low spatial resolution (Bruni et al., 2008).

5.3.3. Positron emission tomography

Positron emission tomography is an improving technology and it is a promising field for the diagnosis of the diseases in relatively early stages. β^+ emitting radioactive isotopes are used in PET imaging (Silindir & Ozer, 2008). The most commonly used PET radionuclides are ^{11}C (half-life ≈ 20 min) and ^{18}F (half-life ≈110 min) (Bonekamp et al., 2010). FDG (flourodeoxyglocose) has proven to be an excellent tracer to detect inflammation in the setting of either infectious or noninfectious processes. The potential of FDG-PET for detecting inflammatory processes in disorders such as regional ileitis, sarcoidosis, rheumatologic disease, and vasculitis and any other disorders is also vast (Alavi et al., 2004). The major shortcomings of this modality include (1) limited availability in most parts of the world, (2) relatively high cost, and (3) difficulty in differentiating malignant tissue from infection or inflammation, although delayed imaging and dual-time-point PET is of considerable help in this regard (Basu et al., 2009). A newer technique that has recently gained favor in clinical use is PET-CT imaging for the rapid detection and localization of occult infection (Petruzzi et al., 2009).

6. Conventional nuclear medicine techniques for infection/inflammation imaging

Conventional nuclear medicine techniques make the use of the following radiopharmaceuticals for infection/inflammation imaging: ^{67}Ga-citrate, ^{99m}Tc or ^{111}In-labeled leukocytes, ^{99m}Tc-labeled granulocyte antibodies, radiolabeled chemotactic peptides, ^{99m}Tc or ^{111}In-labeled

human immunoglobulin (HIG), ^{99m}Tc-nanocolloids, radiolabeled liposomes, cytokines, streptavidin-biotin and ^{18}F-flourodeoxyglocose (^{18}F-FDG).

6.1. ^{67}Ga-citrate

Gallium-67 (^{67}Ga) citrate has been used for detecting infection and inflammation ever since its discovery in 1971 (Kuo et al., 2002). Gallium-67 is a bioisoester of ferric iron with physical half-life of 3.3 days (78 hr) and biologic half-life of 2-3 weeks that binds to serum via transferrin, haptoglobin, albumin and globulins. Gallium attaches to tissues mediated by lactoferrin, as well as lymphocytes and macrophages (Jallilian et al., 2009). Gallium citrate is a radiopharmaceutical used for the detection and staging of some cancers and for identifying inflammation and infection. In the second category, typical indications for ^{67}Ga scanning include sarcoidosis, pneumonia, pyelonephritis, fibrosis, AIDS-related inflammations, osteomyelitis, and fevers of unknown origin (Truluck, 2007). However, this radiopharmaceutical has long physical half-life and high energy gamma radiations, which are unfavourable characteristics for gamma camera imaging and cause high radiation absorbed dose in the patients (Malviya et al., 2007). The specificity of the technique is low, due to physiologic al bowel excretion and accumulation in malignant tissues and areas of bone modeling (Rennen et al., 2002).

6.2. ^{99m}Tc- or ^{111}In-labeled leukocytes

Since the 1970s, scintigraphic imaging with labeled white blood cells has been the most frequently used nuclear imaging method for clinical diagnosis of infection and inflammation worldwide. The success of white blood cell scintigraphy is primarily due to its superb diagnostic accuracy (Signore et al., 2009). Of many radioisotopes used to label leucocytes, Indium-l11 tropolonate (^{111}In) and Technetium-99m hexamethyl propylene amine oxime (^{99m}Tc HMPAO) are the most widely used (Giaffer, 1996). The principal clinical indications for radiolabeled leukocytes include inflammatory bowel disease, osteomyelitis, follow-up of patients with infections of vascular or orthopedic prostheses and soft tissue infections. There has always been concern that chronic infections could be missed using radiolabeled leukocytes, because these infections generate a smaller granulocyte response compared to acute infections (Larverman et al., 2008). Radiolabeled white blood cell (WBC) scintigraphy, enables detection of areas of general inflammation but cannot be used to distinguish between bacterial and nonbacterial inflammatory processes (Sonmezoglou et al., 2001). Although, the radiolabeled leucocytes can be considered as ''gold standard'' that can visualize a majority of infectious and inflammatory lesions, but it is labor-intensive and the *in vitro* labeling carries risks of handling potentially contaminated blood and also requires specialized equipment, taking approximately three hours (Mirshojaei et al., 2011).

6.3. ^{99m}Tc-labeled granulocyte antibodies

Ever since it became clear that labeled leukocytes could visualise infectious foci, investigators have been developing a method that could label leukocytes *in vivo* (Larikka, 2003). For *in vivo* labeling, immunoscintigraphy with ^{99m}Tc labeled monoclonal anti-granulocyte anti-

bodies (AGAb) is used (Gyork et al., 2000). The accumulation mechanism involves nonspecific related uptake of free antibody because of an increased capillary permeability at the focus, with subsequent binding to granulocytes (Lyra et al., 1998). The first approach regarding *in vivo* labeling was the murine IgG1k antibody BW 250/183 (^{99m}Tc-besilesomab, Scintimun®) which recognized the nonspecific cross reacting antigen 95 (NCA-95; also referred to as CD66b and CEACAM8) in the cytoplasm and on the cell membranes of granulocytes and granulocyte precursor cells (Ritcher et al., 2011). Three antigranulocyte antibodies have been tested for infection imaging: anti-NCA-95 immunoglobulin G (IgG) (BW250/183), anti-NCA-90 Fab (Immu-MN3, Leukoscan: anti-CD66), and anti-CD15 (LeuTech). Each of these antigranulocyte antibodies labeled with ^{99m}Tc were determined to accurately delineate infection and inflammation. None of these compounds, however, were specific for infection only (Petruzzi et al., 2009). Fanolesomab is a monoclonal murine M class immunoglobulin that binds to CD15 receptors present on leukocytes. Antibody fragments are appealing because, unlike the whole antibody, they do not induce a human antimouse antibodies (HAMA) response. Sulesomab is a murine monoclonal antibody fragment of the IgG1 class that binds to normal cross-reactive antigen-90 present on leukocytes (Palestro & Love, 2009). Disadvantages of the use of monoclonal antibodies, however, are the high molecular weight, resulting in slow diffusion into sites of inflammation, a long plasma half life and uptake in the liver due to clearance by the reticulo-endothelial system. Use of monoclonal antibodies of murine origin sometimes induces generation of HAMA, which can lead to allergic reactions and altered pharmacokinetics when repeated injections are given. This is, of course, a major limitation for follow-up studies (Larverman et al., 2008). Some radiolabeled mAbs (such as anti-E-selectin and anti-CD4) demonstrated their excellent capability for the localization of inflammatory regions, but lack of their use for the therapeutic purposes, thus limiting their further development and (Malviya et al., 2011).

6.4. ^{99m}Tc- or ^{111}In-labeled chemotactic peptides

Radiolabeled chemotactic peptides are promising tools for the imaging of inflammation and infection. Chemotactic peptides are naturally released by bacteria and initiate leukocyte chemotaxis by binding to high-affinity receptors on the white blood cell membrane. These receptors are present on polymorphonuclear neutrophils and monocytes (Hartwig et al., 1999). The tripeptide, formyl-methionyl-leucyl phenylalanine (f-MLF), is a bacterial product which the initial studies for the design of infection imaging agents focused on the conjugation of f-MLF peptide analogs with the cyclic anhydride of DTPA and radiolabeling with ^{111}In (Babich et al., 2000). The results of radiolabeling of four DTPA derivatized chemotactic peptides analogs established that they are effective agents for imaging sites of infection (Fischman et al., 1991). Small radiolabeled synthetic peptides are currently preferred over proteins and antibodies for imaging applications, since they present several distinct advantages over these biomolecules. Small peptides can be readily synthesized chemically. They can withstand harsher chemical conditions for modification or radiolabeling. They are less likely to induce an immunogenic response. Their plasma clearance is more rapid, yet they often reach a high concentration in the target tissues (Okarvi, 2001). Although ^{111}In and ^{99m}Tc-labeled chemotactic peptides accumulate at sites of infection with high target-to-background

ratios, receptor specificity has not been completely established and a significant amount of localization could be due to nonspecific processes, such as increased tissue permeability, blood pool or blood flow characteristics of inflammatory lesions, or characteristics of the peptides that are not related to For-MLF receptor binding (Babich et al., 1997). However, their development as radiopharmaceuticals has been curtailed because they cause significant leucopenia at physiological concentration (Das et al., 2002).

6.5. ^{99m}Tc- or ^{111}In-labeled Human Immunoglobulin (HIG)

Investigations with monoclonal antibodies by the research group of Rubin et al. led to the discovery of the usefulness of In-IgG scintigraphy for imaging infectious and inflammatory foci (Oyen et al., 1992). Nonspecific polyclonal human immunoglobulins have been shown to localize to sites of infection/inflammation by extravasations from the bloodstream due to the induced local hyperemia and this agent is, thus, nonspecific for infection (Petruzzi et al., 2009). ^{111}In or ^{99m}Tc-labeled HIG has been extensively tested in a large number of clinical studies. It has shown excellent performance in the localization of musculoskeletal infection and inflammation, in pulmonary infection, particularly in immunocompromised patients and abdominal Inflammation. Poor sensitivity of radiolabeled HIG is found in the diagnosis of endocarditis and vascular lesions in general, due to long lasting high levels of circulating activity. A general limitation is the long time span between injection and final diagnosis (24-48 h) (Rennen et al., 2002).

6.6. ^{99m}Tc-nanocolloids

Nanocolloids are colloids of human serum albumin (HAS) less than 50 nm in size, which localize at sites of inflammatory foci through increased capillary permeability (Das et al., 2002). Nanocolloids are good carriers for drugs or radionuclides, the latter can be used for diagnosis or for therapy. Radiolabeled nanocolloids have been widely used in diagnostic nuclear medicine (Lin et al., 2003). Uptake of the tracer is presumably caused by extravasation through the capillary basement membrane, followed by phagocytosis or adsorption of the particles by granulocytes and macrophages (Palestro & Love, 2009). ^{99m}Tc labeled nanocolloids have been most commonly used for marrow and lymphatic imaging and for patient with musculoskeletal infection. The greatest disadvantage is their inability to image infections outside the musculoskeletal system and, as with most of the currently available radiopharmaceuticals, distinguishing infection from inflammation (Das et al., 2002).

6.7. Radiolabeled liposomes

Liposomes are small vesicles consisting of one or more concentric lipid bilayers enclosing discrete aqueous spaces. Liposomes are formed spontaneously when (phospho) lipids are suspended in aqueous media (Larverman et al., 1999). Liposomes have been extensively used as potential delivery systems for a variety of compounds primarily due to their high degree of biocompatibility and the enormous diversity of structures and compositions (Mufamadi et al., 2011). A formulation of liposomes, which is capable of being labeled by both ^{99m}Tc and ^{111}In, simultaneously would have many advantages. This formulation would ena-

ble the acquisition of good early images in the ^{99m}Tc window of the gamma camera and acceptable delayed images in the ^{111}In window (Awasthi et al., 1998). Preliminary studies have shown uptake in sterile and non sterile inflammation (Turpin & Lambert, 2001). Liposomes continue to be very promising carriers for delivery of drugs to inflamed regions of the body, although, to date, no clinical products have specifically taken advantage of the inflammatory targeting of liposomes (Phillips et al., 2009).

6.8. Cytokines

Cytokines are proteins and glicoproteins, members of a family of overlapping and interdependent molecules with important roles in the homeostatic control of the immune system and of pathophysiology of different organs (Signore et al., 2000). Cytokine receptors, usually of high affinity, are normally present at low levels on non-activated cells, but expression is up-regulated during the cell activation and therefore these receptors on the affected tissue are suitable targets for the detection of infection/inflammation (Malviya et al., 2007). Labeled cytokines such as interleukin-1, interleukin-2 and interleukin-8 are a promising class of protein radiopharmaceuticals of small molecular weight (<20 kDa) (Rennen et al., 2001). IL-1, IL-1ra, IL-2, IL-6, IL-8, IL-10, IL-12, p40, interferon γ IFN-γ and epidermal growth factor (EGF) have been radiolabeled for *in vivo* targetting of different leukocyte subsets with promising results for their clinical use. Radiolabeled cytokines, therefore, have the potential for use in the study of the pathophysiology of several diseases and have been used for the diagnosis of inflammation and tumours (Signore et al., 2000). Cytokines and receptor antagonists are specific for inflammation but not for infection (Das et al., 2002).

6.9. Streptavidin-biotin

The biotin-straptavidin system has been used for many years in a varity of different applications (Diamandis & Christopoulos, 1991). Streptavidin is a protein extracted from the bacterium *Streptomyces avidinii* with a molecular weight of 60 kDa and has four binding sites with high affinity ($K_D = 10^{-15}$ M) for biotin, which is a water soluble vitamin with a molecular weight of 244 kDa (Kittigul et al., 1998). Avidin/indium-111 biotin scintigraphy is based on the non-specific accumulation of avidin at sites of inflammation or infection, linked to increased transcapillary leakage of macromolecules and to interstitial oedema at these sites. Due to its extremely high affinity for and low dissociation constant with biotin, sites of infection can be imaged using avidin as a pre-target, followed by ^{111}In-labeled biotin (Lazzeri et al., 1999). The potential of radiolabeled biotin as an infection imaging agent has already been shown in an experimental animal model of infection using biotin labeled with fluorine-18 as well as in a small group of patients with osteomyelitis using ^{111}In-labeled biotin (Lazzeri et al., 2008). Because, the mechanism of localization is nonspecifically, based on the increasing vascular permeability, this radiopharmaceutical is not specific for infection imaging.

6.10. ^{18}F-flourodeoxyglocose (^{18}F-FDG)

A number of positron emitting radioisotopes are available for clinical use but the one most commonly used is 18 Fluorine fluorodeoxyglucose. FDG is an analogue of glucose which

concentrates in areas of high glycolytic activity such as rapidly dividing cells. Neutrophils and macrophages have increased FDG uptake allowing localization of infection and inflammation (Robinson & Scarsbrook, 2009). PET with fluorine-18 fluorodeoxyglucose is a powerful molecular imaging technique that allows areas with different pathologies such as malignant neoplasias and active inflammation in clinical human studies to be assessed (Wyss et al., 2004). Numerous reports have demonstrated increased FDG uptake at the sites of infection and inflammation. FDG-PET is very helpful in the evaluation of chronic osteomyelitis, sarcoidosis, fever of unknown origin (FUO), and differentiating toxoplasmosis from lymphoma in the central nervous system in HIV-positive patients. Despite all of these findings, however, FDG-PET has not been fully accepted as an effective way to evaluate infection and inflammation (Zhuang et al., 2005). This is nonspecific since ^{18}F-FDG is also taken up at non-specific sites of inflammation as well as sites of tumor (Petruzzi et al., 2009).

7. Properties of an ideal infection imaging agent

The ideal radiopharmaceutical should enable early diagnostic imaging, a low absorbed radiation dose and make a distinction between inflammation and infection, which is of paramount importance in the field of various infections including musculoskeletal, soft-tissue and parenchymal infections. Furthermore, it should be nontoxic, inexpensive, readily available, and rapidly cleared from the blood and the body (Gemmel et al., 2009). The preparation of the radiopharmaceutical should be quick and easy, preferably with technetium-99m as the radionuclide (Larverman et al., 2008). Low levels of accumulation in bowel and blood pool are particularly important characteristics of such an agent. Focal accumulation or transient activity in the bowel would make detection of infections in this area very difficult. Similarly, high blood pool activity increases background and complicates the imaging of vascular infections (Babich & Fischman, 1999). These properties for an ideal infection imaging agent are shown in Table 1 (Gemmel et al., 2009).

1. Rapid localization and good retention at the site of infection
2. Rapid clearance from non infected tissues (high target to background ratio)
3. Uptake in infection not in sterile inflammation, identifyingbacterial, viral and fungal infections.
4. The uptake of radiotracer should be proportional to the degree of infection. Therapy response can be monitored.
5. No pharmacological effect/immunological response, saferepeated injection.
6. Labeling should be simple and uncomplicated and wellcharacterized
7. ^{99m}Tc labeling is preferable, positron labeling is still experimental
8. Not depending on host leukocyte function
9. Less expensive than other combined modalities

Table 1. The requirements for an ideal radiopharmaceutical for infection imaging

http://dx.doi.org/10.5772/52882

Considering these criteria for an ideal radiopharmaceutical for infection imaging, the best techniques which fit this criteria better, are following by next topic.

8. Targeting nuclear medicine techniques in microorganisms imaging

The theoretical advantage of using an antimicrobial agent as the localizing agent for infective foci is the selective toxicity of the compound for microbes rather than human targets. Such agents should therefore be able to distinguish between inflammation due to infection with microbial pathogens, and inflammation due to immune activity i.e. autoimmune disease where microbes are not involved (Wareham et al., 2005). There is now a wide range of radiolabeled antimicrobial agents that are undergoing evaluation. The first group consists of radiolabeled antibiotics such as ^{99m}Tc- or 18F-ciprofloxacin, ^{99m}Tc-sparfloxacin, ^{99m}Tc-ceftizoxime and anti-fungal agents such as ^{99m}Tc-fluconazole and ^{99m}Tc-isoniazid and the anti-*Mycobacterium tuberculosis* agent ^{99m}Tc-ethambutol. The second group of radiopharmaceuticals for imaging infections is derived from the array of human antimicrobial peptides/proteins that binds to specific bacterial antigens, e.g. peptides derived from human lactoferrin, ubiciquidin and human neutrophil peptide 1–3 (^{99m}Tc-HNP1–3; members of the α-defensins) (Signore et al., 2008).

8.1. Antibiotics

In 1945, Selman Waksman proposed that the word antibiotic can be defined as ''a chemical substance of microbial origin that possesses antibiotic powers'' (Davies, 2006). Antibiotics are drugs of natural or synthetic origin that have the capacity to kill or inhibit the growth of micro-organisms. Antibiotics are sufficiently non-toxic to the host are used as chemotherapeutic agents in the treatment of infectious diseases of humans, animals and plants (Hernandez Serrano, 2005). Antibiotics are designed to support host defense in controlling infection (Kristian et al., 2007). Most antibiotics used in human treatment were originated from natural templates produced by particular species of bacteria or fungi as a mechanism of competition to ensure their own survival (e.g., to gain a larger share of environmental food supplies by killing competitors (Hancock, 2005).

8.1.1. Types of antibiotics

Antimicrobial drugs are classified according to their mechanism of action, for example, cell wall inhibiting, cell membrane inhibiting, protein synthesis inhibiting and nucleic acid inhibiting (Riaz et al., 2011). The major targets for the main classes of antibiotics include cell membranes (e.g., mupirocin), cell-wall biosynthesis enzymes and substrates (e.g., beta-lactams, vancomycin, and bacitracin), bacterial protein synthesis (e.g., chloramphenicol, tetracyclines, macrolides, clindamycin, aminoglycosides, linezolid, mupirocin, and fusidic acid), and bacterial nucleic acid replication and repair (e.g., co-trimoxazole [trimethoprim/sulfamethoxazole], which acts via an anti-metabolite mechanism, rifampicin, and quinolones) (Hancock, 2005).

8.1.2. Mechanisms of antibiotics action

Antibiotics interfere with the growth of bacteria by undermining the integrity of their cell wall or by interfering with bacterial protein synthesis or common metabolic pathways. The terms bactericidal and bacteriostatic are broad categorizations, and may not apply for a given agent against all organisms, with certain antimicrobials being bactericidal for one bacterial pathogen but bacteriostatic for another (Niederman, 2009). Bacteriostatic agents inhibit the growth of bacterial cells but do not kill them, whereas bactericidal agents kill the bacteria. However, these categories are not absolute, since the killing effect of the drug varies with the test method and the species being tested. Agents may be bactericidal against one group of organisms and bacteriostatic against another) (French, 2006). Bactericidal antibiotics, such as the beta-lactams (including the cephalosporins, carbapenems, and cephems), glycopeptides (including vancomycin), fluoroquinolones, polymyxins, and the lipopeptide daptomycin, are often preferred for treatment of these diseases, particularly for cases of febrile neutropenia, meningitis, and endocarditis (Hancock, 2005). The importance of bactericidal drugs versus bacteriostatic drugs in the treatment of infections has been debated for many years. Although the advantages of bactericidal agents appear obvious (e.g., rapid elimination of bacteria and a decreased possibility of resistance development or infection recurrence), bactericidal activity could be undesirable in some clinical settings. In CNS (central nervous system) infection, for example, the sudden lysis of bacteria by a bactericidal agent leads to a sudden increase in bacterial products (e.g., lipopolysaccharide in gram-negative organisms or peptidoglycans in gram-positive organisms) that may stimulate cytokine production, causing potentially harmful inflammation (Finberg et al., 2004).

8.1.3. Review on radiolabeled antibiotics

Agents that specifically target the infectious organisms (e.g., bacteria, fungi or viruses) have potential to distinguish microbial from non microbial inflammation (Boerman & Nijmegen, 2008). The first and most intensively studied agent in this category is ^{99m}Tc-ciprofloxacin (^{99m}Tc-infecton), a member of fluoroquinolone group that was introduced by Solanki et al. as a new class of radiopharmaceutical for infection imaging in 1993 (Solanki et al., 1993). The results of 99mTc-infecton clinical application in imaging patients with various infections are shown in Table 2.

Moreover, radiolabeling of some other quinolone antibiotics, cephalosporines, antifungal agents, anti *mycobacterium tuberculosis* and also antiviral radiopharmaceuticals for targeting diagnosis of infectious foci, were investigated up to now.

8.1.3.1. Radiolabeled antibacterial agents

The use of radiolabeled antibiotics is fast emerging as a promising diagnostic test for the detection of infective lesions, because of their specific binding to the bacterial component (Singh et al., 2005). The first clinical application of ^{99m}Tc-ciprofloxacin was performed by Vinjamuri et al. in 1996 and the ability of ^{99m}Tc infecton imaging in comparison with radiolabeled white blood cell imaging for evaluating of bacterial infection, were investigated (Vin-

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Type of infection	Number of patients	Sensitivity (%)	Specificity (%)	Reference
Known or suspected sites of infection	56	84	96	Vinjamuri et al., 1996
Various infections with proven microbiological tests	99	83	91	Britton et al., 1997
Suspected of a variety of infections	90	70.3	93.1	Hall et al., 1998
Suspected orthopaedic infection	15	85	92	Yapar et al., 2001
Clinically suspected chronic skeletal infection	51	63	96	Sonmezoglo et al., 2001
Suspected bacterial infection	879 (in 8 country under the auspices of the IAEA)	85.4	81.7	Britton et al., 2002
Proven or suspected bone infection	45	97.2	80	Malamitsi et al., 2003
Suspected septic arthritis or osteomyelitis	27	100	37.5	Sarda et al., 2003
Postoperative spinal infection	48	52	79	De Winter, et al., 2004
Acute or chronic cholecystitis based on the clinical and ultrasonographic findings	60	91.7	75	Cho et al., 2007

Table 2. Some reported clinical applications of ^{99m}Tc-ciprofloxacin (infecton).

jamuri et al., 1996). The results showed 84% sensitivity and 96% specificity of ^{99m}Tc ciprofloxacin in contrast to 81% sensitivity and 77% specificity of white blood cell imaging. Ciprofloxacin has several advantages over radiolabeled leucocytes, and other methods for imaging infection, which include the following: (1) specificity for infection, (2) lack of bone marrow uptake, which is a significant advantage in imaging bone and joint and orthopedic prostheses infections, (3) ease and cost of preparation of the agent, (4) *ex vivo* labeling, which avoids contact with blood and hence the risk of acquiring blood borne infections such as HIV and hepatitis B and C, (5) independence of the host inflammatory response and neutrophil count and hence it can be used to image infections in immunocompromised patients, including those who are neutropaenic, where culture is often negative and white blood cell imaging unreliable and (6) availability in a kit format with long shelf-life, making it user friendly and more widely available (Akhtar et al., 2012). However, the low binding affinity of ^{99m}Tc-ciprofloxacin to bacteria and the risk of emerging antibiotic-resistant microorganisms make this radiopharmaceutical unattractive for imaging bacterial infections (Welling et

al., 1999). The majority of other fluoroquinolone antibiotics, some of the cephalosporins and also other antibacterial agents were radiolabeled up to now for bacterial infection imaging with promising results (Table 3).

Antibiotic	Antimicrobial group	Radio-nuclide	Microorganisms	Target to non target ratio (T/NT)	Reference
Ceftizoxime	Cephalosporine- third generation	Tc-99m	*Escherichia coli*	3.24	Gomes Barreto et al., 2000, 2005
Floclunazol	Antifungal	Tc-99m	*Candida albicans -Aspergillus fumigates*	3.6	Lupetti et al., 2002
Isoniazid	Antituberclosis	Tc-99m	*Mycobacterium tuberculosis*	-	Singh et al., 2003
Enrofloxacin	Fluoroquinolone-second generation	Tc-99m	*Staphylococcos aureus* and *Candida albicans*	4.25	Siaens et al., 2004
Vancomycin	Glycopeptide antibiotic	Tc-99m	*Staphylococcos aureus 25923*	5	Roohi et al., 2005
Pefloxacin	Fluoroquinolone-second generation	Tc-99m	*Escherichia coli*	5.6	El Ghany et al., 2005
Ethambutol	Antituberclosis	Tc-99m	*Mycobacterium tuberculosis*	-	Verma et al., 2005
Kanamycin	Aminoglycoside	Tc-99m	*Staphylococcos aureus 25923*	2.5	Roohi et al., 2006
Cefoperazone	Cephalosporin-forth generation	Tc-99m	*Staphylococcus aureus*	4.5	Motaleb, 2007a
Lomefloxacin	Fluoroquinolone-second generation	Tc-99m	*Staphylococcus aureus*	6.5	Motaleb, 2007b
Ofloxacin	Fluoroquinolone-second generation	Tc-99m	*Staphylococcus aureus*	4.3	Motaleb, 2007b
Sparafloxacin	Fluoroquinolone-third generation	Tc-99m	*Staphylococcus aureus*	5.9	Motaleb, 2009
Cefuroxime axetil	Cephalosporin-second generation	Tc-99m	*Staphylococcus aureus*	2.5	Yurt Lmbrecht et al., 2008a
Linezolid	Oxazolidinone	I-131	*Staphylococcus aureus*	5.5	Yurt Lmbrecht et al., 2009

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Antibiotic	Antimicrobial group	Radio-nuclide	Microorganisms	Target to non target ratio (T/NT)	Reference
Moxifloxacin	Fluoroquinolone-forth generation	Tc-99m	*Escherichia coli*	6.8	Chattopadhyay et al., 2010
Norfloxacin	Fluoroquinolone-second generation	Tc-99m	*Staphylococcus aureus*	6.9	Ibrahim et al., 2010
Rifampicin	Rifamycin group	Tc-99m	Methicillin-resistant *Staphylococcus aureus*	7.34	Shah et al., 2010
Ceftriaxone	Cephalosporin- third generation	Tc-99m	*Escherichia coli*	5.6	Mostafa et al., 2010
Gemifloxacin	Fluoroquinolone-forth generation	Tc-99m	*Streptococcus pneumoniae*	4.88	Shah & Khan, 2011a
Rufloxacin	Fluoroquinolone-second generation	Tc-99m	*Staphylococcus aureus*	6.04	Shah & Khan, 2011b
Clinafloxacin	Fluoroquinolone-forth generation	Tc-99m	*Staphylococcus aureus*	4.96	Shah & Khan, 2011c
Nitrofurantoin	Nitrofuran derivatives-DNAinhibitors	Tc-99m	*Escherichia coli*	4.84	Shah et al., 2011a
Garenoxacin	Fluoroquinolone-forth generation	Tc-99m	multi-resistant *Staphylococcus aureus* (MRSA) --penicillin-resistant *Streptococci* (PRSC)	5.2 5.4	Shah et al., 2011b
Cefotaxime	Cephalosporin- third generation	Tc-99m	*Staphylococcus aureus*	2.98	Mirshojaei et al., 2011
Gatifloxacin	Fluoroquinolone-forth generation	Tc-99m	*Escherichia coli*	4.5	Motaleb et al., 2011
Cefepime	Cephalosporin- forth generation	Tc-99m	*Escherichia coli*	8.4	Motaleb et al., 2011
Levofloxacin	Fluoroquinolone-third generation	Tc-99m	*Staphylococcus aureus*	17.2	Naqvi et al., 2012

Table 3. The history of radiolabeled antibiotics applied in infection imaging.

8.1.3.2. Radiolabeled antituberculous agents

Mycobacterial infections have been shown to be increasing in number worldwide, mainly due to a global increase in developing countries, the increased number of patients with HIV infection and AIDS disease worldwide, an increasing the number of elderly patients and the emergence of multidrug resistant tuberculosis (De Backer et al., 2006). Tuberculosis is an ancient infectious disease that remains a threat for public health around the world. Although the etiological agent as well as tuberculosis pathogenesis is well known, the molecular mechanisms underlying the host defense to the bacilli remain elusive (Jordao & Vieira, 2011). A suitable ligand, ethambutol (EMB) that is, specific first line antitubercular drug was chosen for detection as well as localization of the lesion using nuclear medicine modality. ^{99m}Tc-EMB was used in humans for tubercular imaging. The mycobacterial lesion uptake study carried out so far in humans suggested that ^{99m}Tc-EMB is specific and sensitive radiopharmaceutical for sensitive as well as resistant tubercular lesion detection and localization (Singh & Batnagar, 2010). Isoniazid is another antituberculous agent that binds to mycolic acid in the cell walls of living mycobacteria. Successful imaging of *Mycobacterium tuberculosis* cold abscesses in rabbits was reported along with rapid washout from *Staphylococcos aureus* infected abcesses suggesting the agent my be very useful for the detection and follow up of tuberculous lesions in humans (Wareham et al., 2005). Ethambutol was successfully labeled with ^{99m}Tc followed by studies on mice and rabbits for labeling efficiency, *in vitro* and *in vivo* stability, blood kinetics, and organ distribution (Table 3). Therefore it was concluded that this radiolabeled agent can be used for detection and follow up of tuberculous lesions in patients especially to determine the treatment endpoint of antituberculous drugs (Akhtar et al., 2012).

8.1.3.3. Radiolabeled antifungal agents

During the past two decades, invasive fungal infections have emerged as a major threat to immunocompromised hosts. Patients with neoplastic diseases are at significant risk for such infections as a result of their underlying illness and its therapy (Shoham & Levitz, 2005). *Candida albicans* is the most common fungal pathogen, and is the organism responsible for the majority of localized fungal infections in humans (De Assis et al., 2008). Fluconazole is the most frequently employed among the triazole antifungal agents in treating *Candida* infections in individuals with severe immunodeficiency (Lupetti et al., 2011). It was successfully labeled with ^{99m}Tc by Lupetti et al., in 2002. This labeled compound successfully detected infections with *Candida albicans* but not bacterial infections or sterile inflammatory sites in animals (Table 3) (Lupetti et al., 2002). In the attempt to develop new tracers that specifically detect fungal infections, components of fungal cell wall have been considered highly selective targets. Since chitin is a component of fungal cell wall, which is absent in mammalian cells, a radiolabeled marker for chitine, ^{123}I-chitinase was developed in order to bind specifically to fungal cells (Lupetti et al., 2011). It was tested for specificity in a mouse model to localize fungal infections with both *Candida* and *Aspergillus* species. Furthermore, the chitinase uptake appeared to correlate well with the number of viable fungal cells (Gemmel et al., 2009). The results revealed that this radioiodine labeled enzyme accumulates in *Candida albicans* and *Aspergillus fumigatus* infections in mice; these infections can be visualized at 24 h after injection of the tracer and its accumulation, correlates with the number of viable fungal cells without visualizing bacterial infections or sterile inflammations (Lupetti et al., 2011).

8.1.3.4. Radiolabeled antiviral agents

Antiviral therapeutics deals specifically with the treatment of viral infections and refers to the use of drugs and the methods of the execution in the treatment of life-threatening viral diseases (Saxena et al., 2009). Development of a suitable radiolabeled antiviral drug probe must take into account the specificity of metabolism of the drug by virus-infected cells, the capability and convenience of labeling the drug without altering that specificity, and the biodistribution of the drug (Price et al., 1983). The possibility of using a naturally occurring virus-encoded molecule as an imaging reporter was first explored in the early 1980s, when acyclovir was approved as an antiviral drug for the treatment of HSV (herpes simplex virus) infections. The ability of this and other nucleoside analogues to selectively inhibit HSV replication is based on their ability to undergo phosphorylation by the viral thymidine kinase (TK), but not by corresponding host enzymes (Bray et al., 2010). Ideally, the drug to be used should be phosphorylated exclusively by viral TK and, therefore, label only infected cells (Price et al., 1983). Among various substrates, radiolabeled 2′-fluoro-2′-deoxy-5-iodo-1-β-D-arabinofuranosyluracil (FIAU) demonstrated high sensitivity and selectivity for the detection of HSV1-tk expression. FIAU is trapped intracellularly only in the presence of HSV1-tk (Bengel et al., 2000). Another antiviral drug, 2'-fluoro-5-methyl-1-beta-D-arabinosyluracil labeled with carbon 14 ([^{14}C]FMAU), was used as a probe for selectively imaging brain infection in a rat model to diagnosis of herpes simplex encephalitis by quantitative autoradiography (Saito et al., 1984). Stavudine, 2′, 3′ didehydro-3′-deoxythymidine (d4T), is a synthetic thymidine nucleoside analog that is effective in the treatment of human immunodeficiency virus (HIV) infection. Stavudine enters cells rapidly by nonfacilitated diffusion, with the rate of influx being linear with respect to concentration. This potent antiviral agent was radiolabeled with ^{11}C and the results showed that future PET studies with this radiopharmaceutical will allow in vivo measurements of the pharmacokinetics of stavudine in both animal models and human subjects (Livni et al., 2004). The replication cycles of various DNA and RNA viruses offer a variety of targets for drugs and probes that interact specifically with virus-encoded molecules which made candidate tracers of different virus families for virus-specific imaging (Bray et al., 2010).

8.2. Antimicrobial peptides

Antimicrobial peptides are widespread in living organisms constitute an important component of innate immunity to microbial infections. By the early 1980s, more than 800 different antimicrobial peptides had been isolated from mammals, amphibians, fish, insects, plants and bacterial species. In humans, they are produced by granulocytes, macrophages and most epithelial and endothelial cells (Kamysz, 2005). Antimicrobial peptides usually contain hydrophobic and cationic amino acids, which are able to organize in an amphipatic structure (Lupetti et al., 2003a). They can be expressed constitutively or induced during inflammation or microbial challenge. Antimicrobial peptides displayed antibacterial, antiviral and antifungal activities *in vitro* and were effective in experimental infections with multidrug resistant *Staphylococcus aureus* and *Mycobacterium tuberculosis* (Lupetti et al., 2003b). Due to the development of microorganisms' resistant to the most widely used antibiotics and antifun-

gal agents, antimicrobial peptides have gained renewed attention as possible therapeutic candidates (Lupetti et al., 2003c). Difficulties arising in purifying natural antimicrobial peptides from various sources have prompted the recombinant production of antimicrobial peptides by genetically engineered bacteria or by peptide synthesis. Such methods result in sufficient amounts of antimicrobial peptides produced under good laboratory practice conditions, which is essential for future approval to use the peptides in clinical trials. Peptide synthesis also allows the production of chemical variants, such as denantiomers, peptides that have amino acid substitutions at various positions, and peptide libraries (Lupetti et al., 2003b). Synthetic peptides are usually small, rapidly removed from the circulation and other body compartments, and flexible, because they do not hold a particular structure in a hydrophilic environment, and display a favorable adverse effect profile (Akhtar et al., 2012).

8.2.1. Types of antimicrobial peptides

Antimicrobial peptides usually contain less than 50 amino acids with a net positive charge due to an excess of basic residues, such as lysine and arginine, and approximately 50% hydrophobic amino acid (Lupetti et al., 2003c). According to combination of sequence homologies, three dimensional structures and functional similarities classification, antimicrobial peptides can be divided into 5 main classes: (1) linear, mostly α-helical peptides without cysteine residue, with or without hinge region (bombinins, cecropins, magainins), (2) antimicrobial peptides with one disulfide bond that form a loop structure with a tail (bactenecins, esculentins), (3) antimicrobial peptides with two or more disulfide bonds giving mainly or only β-sheet structure (defensins, protegrins), (4) linear peptides without cysteine residue and with an unusual composition of regular amino acids (histatins, indolicidin, temporins) and (5) antimicrobial peptides derived from larger peptides or proteins with other known functions (lactoferricins, MUC7). Despite differences in structure, all the peptides display a similar motif: an amphiphilic structure, with one surface being highly positive and the other hydrophobic (Kamysz, 2005). Ubiquicidin 29-41 (UBI) is a fragment of the cationic antimicrobial peptide that is present in various species including humans (Melendez-Alafort et al., 2003). Short peptides from lactoferrin (a 692-amino acid iron-binding protein found in body fluids, secretary granules of neutrophils and mucosal epithelium), consist of HLF (human lactoferrin peptide) 1-11 and 2-11, were tested for their ability to target infections (Knight, 2003). One of the best-studied antimicrobial peptides is human neutrophil peptide (HNP)-1, which is a member of the family of defensins. This antimicrobial peptide, which is stored in the granules of human neutrophils, contributes to bacterial killing during phagocytosis. HNP-1 displays antimicrobial activity against gram-positive and gram-negative bacteria, many fungi and some enveloped viruses (Welling et al., 1999). Bacteriocins are ribosomally synthetized antimicrobial peptides produced by bacteria (Oscariz & Pisabarra, 2001). Bacteriocins are peptides secreted by cells to inhibit or kill closely related species. They are divided into two basic types. The first group comprises peptides which have been subjected to post-translatory treatment (modified bacteriocins-lantibiotics). The second group includes unmodified bacteriocins. Furthermore, bacteriocins comprise colicins and microcins, i.e. peptides produced by Gram-negative bacteria (e.g., *Escherichia coli*) (Kamysz, 2005).

http://dx.doi.org/10.5772/52882

8.2.2. Mechanisms of antibacterial peptides action

Although the exact mechanism of action of antimicrobial peptides (AMPs) remains a matter of controversy, there is a consensus that these peptides selectively disrupt the cell membranes and the amphipathic structural arrangement of the peptides is believed to play an important role in this mechanism (Peddy et al., 2004). Based on the available data, all proposed modes of action have implicated the cationic and hydrophobic nature of the AMPs in its initial interaction with the negatively charged lipids in bacterial membranes while some variations are expected in non-bacterial targets. Due to their cationic nature, AMPs are electrostatically attracted to negatively charge microbial surfaces such as lipopolysaccharide (LPS) in Gram-negative bacteria and teichoic and teichuronic acids in Gram-positive bacteria (Rotem & Mor, 2009). Insertion of the peptides into the bacterial cytoplasmic membrane under the influence of the transmembrane electrical potential gradient results in transient permeability of membranes and leakage of cellular constituents, such as potassium ions, thus destroying the proton gradient across the membrane, resulting in bacterial cell death (Lupetti et al., 2003c).

8.2.3. Review on radiolabeled antibacterial peptides

Because antimicrobial peptides preferentially bind to bacterial membranes, radiolabeling of these peptides would offer the medical community the novel candidates for the development of bacteria-seeking radiopharmaceuticals (Welling et al., 1999). A number of radiolabeled peptides have been evaluated for the scintigraphic detection of infections (Table 4). Among the most specific ones are technetium-99m labeled cationic antimicrobial peptides derived from ubiquicidin (UBI) that preferentially bind to microorganisms (Welling et al., 2004). ^{99m}Tc-labeled ubiquicidin 29-41 (^{99m}Tc-UBI 29-41) is a highly sensitive and specific agent for the scintigraphic detection of bacterial and fungal infections in animals and humans. ^{99m}Tc-UBI 29-41 allows rapid visualization of Gram-positive and Gram-negative bacterial infections with little or no accumulation in sterile inflammatory processes, indicating that this peptide directly tags the microorganisms at the site of infection (Vallejo et al., 2008). Tc-99m labeled antimicrobial peptides UBI 29-41, UBI 18-35, UBI 31-38, hLF 1-11, and defensins accumulate significantly in tissues infected with Gram-positive and Gram-negative bacteria and *Candida albicans*. Significantly lower accumulation of these peptides occurs in sterile inflamed tissues (Fard-Esfahani et al., 2010). The peptides hLF 1-11 and 2-11, when labeled with ^{99m}Tc by a direct reduction technique, bound well to bacterial cells *in vitro*. Unlike ^{99m}Tc-UBI peptides, however, the labeled hLF peptides also bound to human leukocytes. This makes them less useful for infection imaging, because they cannot adequately discriminate between bacterial infection and sterile inflammation. Furthermore, the peptides had a relatively high degree of hepatobiliary clearance (Knight, 2003). There are limitations attributed to synthesis/isolation of antimicrobial peptides, labeling with isotopes, minimum detection limit of 10^3 Colony-Forming Unit (CFU) of bacteria, and inability to distinguish between bacterial and fungal infections. In addition, different bacterial types reveal different tracer accumulation (*Staphylococcus aureus* versus *Escherichia coli*). Currently no evidence regarding resistance against antimicrobial peptides has been reported. Considering the merits and demerits of radiolabeled peptides and radiolabeled antibiotics, it can currently be con-

cluded that radiolabeled peptides are better specific infection localizing agents than radiolabeled antibiotics (Akhtar et al., 2012).

Antimicrobial Peptides	Radionuclide	Microorganisms	Experimental model	Reference
Human neutrophil peptide (HNP) -1	Tc-99m	*Staphylococcus aureus* -*Klebsiella pneumoniae*	Swiss mice	Welling et al., 1999
Ubiquicidin (UBI) 29–41 -UBI 18–35 -UBI 31–38 -Human lactoferrin (hLF) 1–11 -Defensins	Tc-99m	Multidrug-resistant *Staphylococcus aureus (MRSA)* -*Klebsiella pneumonia* -Fluconazole resistant *Candida albicans*	Swiss mice -New Zealand White rabbits	Welling et al., 2001
UBI 29-41	Tc-99m (HYNIC- or N2S2-chelate conjugated)	*Staphylococcus aureus* -*Klebsiella pneumonia*	Swiss mice	Welling et al., 2003
UBI 29-41 hLF 1-11	Tc-99m	*Staphylococcus aureus* -MRSA	Swiss mice -Wistar rats	Nibbering et al., 2004
UBI 29-41 (in a kit formulation)	Tc-99m	*Staphylococcus aureus* -*Escherichia coli*	Rabbits	Akhtar et al., 2004
UBI 29-41	Tc-99m	Various bacterial microorganisms	Human (with suspected bone infection)	Melendez-Alafort et al., 2004
UBI 29-41	Tc-99m	Various bacterial microorganisms	Human (with soft tissue infection and osteomyelitis)	Akhtar et al., 2005
UBI 29-41	Tc-99m	*Staphylococcus aureus* (prosthetic joint infection)	New Zealand rabbits	Sarda-Mantel et al., 2007
hLF 1–11	Tc-99m	MRSA	Swiss mice	Brouwer & Welling, 2008
UBI 29-41	^{99m}Tc/Tricine/ HYNIC^{0} from lyophilized kits	Various bacterial microorganisms	Human (with suspected bone or soft-tissue infections)	Gandomkar et al., 2009
UBI 29-41	Tc-99m	Various bacterial microorganisms	Human (with diabetic foot infection)	Fard-Esfahani et al., 2010

Table 4. Some reported applications of antimicrobial peptides as infection imaging agents.

http://dx.doi.org/10.5772/52882

9. Antibiotics and antimicrobial peptides radiolabeling

A simple, efficient and reproducible radiolabeling procedure is essential to develop radiopharmaceuticals for routine clinical use (Gandomkar et al., 2009). The various methods of radiolabeling with ^{99m}Tc, including the direct labeling methods for antibiotics and peptides and indirect labeling of peptides using the bifunctional chelating agents have been discussed. The radionuclide should be firmly attached or incorporated into the peptide to allow the visualization of the target and reliable assessment of its pharmacokinetics after its intravenous administration. Moreover, the labeling conditions should not affect the binding activity of the peptide to the microorganism (Lupetti et al., 2003c).

Quality assurance is the sum of all parameters concerning the preparation and control of a finished product. Biological quality control of pharmaceutical products becomes essential as they are ultimately to be consumed by living organisms, in particular the humans (Patei Riddhi et al., 2011). Radiochemical purity and labeling efficiency analyses techniques are performed by high performance liquid chromatography (HPLC), C18-Sep-pak, instant thin layer chromatography (ITLC) and paper chromatography (IAEA-TECDOC-1414, 2004). Optimum condition of labeling are required for maximum labeling of ^{99m}Tc-conjugates by optimizing the affecting factors on radiolabeling such as: pH, the amount of reducing agent and incubation time of reaction mixture. Moreover, the stability of radiolabeled complex in human blood serum and room temperature are determined. The biodistribution study of labeled complex is done by percent uptake calculation of the tracer at various organs of experimental animal, after intravenous administration of the radiopharmaceutical at different intervals to monitor the distribution style of radio complex at different organs, localization and high uptake at target site without any accumulation in vital organs.

9.1. Direct labeling

The direct labeling method is a simple procedure in which the peptide is labeled in absence of an exogenous chelator (Lupetti et al., 2003b). The direct approach is characterized by poorly defined chemical structures, and it is generally thought that the 99mTc binds to the sulfhydryl groups produced by reduction of the peptide disulfide bridge. Therefore, peptides containing cysteine seem to be a basic requirement for this labeling approach (Melendez-Alafort et al., 2009). The various complexes of ^{99m}Tc may be formed by interaction between electron donor atoms and reduced technetium. In the case of antibiotics radiolabeling, in order to form bonds with technetium, the structure must contain electron donors such as oxygen, nitrogen and sulfur. The labeled complex may be formed electron pairs of these atoms with reduced technetium that is +1 or +3 in the reduced states similar to other studies (Yurt Lambrechtet al., 2008b).The mechanism underlying the direct labeling method is not fully elucidated, but it probably involves the reduction of ^{99m}Tc-pertechnetate by stannous ions and KBH_4, the production of a TcO (pyrophosphate) intermediate, and the substitution reaction transferring the reduced technetium from this intermediate to the amino groups of cationic peptides. The end-product from this reaction could be a reduced metal (N4) complex, as reported for many tetrapeptides (Lupetti et al., 2003c).

9.2. Indirect labeling

Indirect method of labeling is used mostly for radiolabeling of peptides and it is not common for antibiotics labeling. A widely used method for labeling of small peptides is by conjugation of bifunctional chelators to the peptide and several attampts have been made using hydrazinonicotinamid (HYNIC) and N_3S compounds (S-benzoyl MAG3) (IAEA-TEC-DOC-1414, 2004). Among the various bifunctional chelating agents developed to date, HYNIC constitutes a representative agent for ^{99m}Tc radiolabeling. Since HYNIC serves as a monodentate or bidentate ligand, a coligand is necessary to complete the coordination sphere of the technetium core. Tricine is often used as the coligand because of the production of ^{99m}Tc-HYNIC-labeled peptides and polypeptides with high radiochemical yields and high specific activities in a short reaction time (Ono et al., 2001). Moreover, the indirect labeling method permits post conjugation labeling, whereby the peptide is first conjugated to the BFCA and then stored and labeled when required for clinical use. Furthermore, this approach is the only choice for peptides containing disulfide bridges essential for receptor recognition (Melendez-Alafort et al., 2009).

10. Conclusion

Nuclear medicine technology offers an attractive option for diagnosis of focal infections due to its sensitivity based on pathophysiological and pathobiochemical processes. This approach needs a reliable radiopharmaceutical that can concentrate in site of infection with high specificity. As reviewed in this chapter, various conventional radiopharmaceuticals which are basically on the uptake mechanism of targeting host inflammatory response are not specific for infection imaging. In contrast, the use of radiopharmaceuticals for specific targeting of microorganisms responsible for infection, have been proposed. In this respect, radiolabeled antibiotics and antimicrobial peptides, by specific binding to the bacterial component, have the potential to distinguish microbial from non infectious inflammation at the early stage of diseases. However, according to the irregular usage of antibiotics and increasing antibiotic-resistant microorganisms, it seems that antimicrobial peptides have more advantages over antibiotics. We suggest that, antimicrobial peptides with wide promising properties as the infection imaging agents have the ability to be used in clinical usages in patients with suspected infections for more accurate diagnosis.

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