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Radiopharmaceuticals for infection imaging

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ABSTRACT: Infectious diseases hold significant global importance, resulting in millions of deaths annually and spreading so swiftly that they present a global public health threat. Diagnosis of infections is usually based on a detailed anamnesis, physical examination, as well as laboratory evaluation, and imaging methods. Nuclear medicine and radionuclide imaging have gained a significant role in the diagnosis of infection in the last decades, mainly due to the restrictions and limitations of conventional diagnosis methods in detecting and diffracting sterile inflammation and infection. In recent years different agents such as peptides, aptamers, and antibodies have been investigated for infection imaging due to the success they accomplished in radio imaging diagnosis of different diseases. In this review, currently used and novel tracers for infection/inflammation imaging have been summarized and their advantages and disadvantages have been reviewed for further possible studies.

KEYWORDS: Infection; diagnosis; radiolabeled peptides; radiolabeled aptamers; radiolabeled antibodies; radiolabeled antibiotics.

1. INTRODUCTION

Infection and Inflammation imaging is one of the application areas of nuclear medicine. The complex response of the body to any stimulus (physical, chemical, immunological, radiation) to bring the serum molecules and/or cells of the immune system to the injured site is called inflammation, and if a microorganism includes in this process, it is called infection [1]. Microorganisms that live naturally in the body are not considered infections. Most microorganisms generally do not harm human health, but pathogenic microorganisms such as viruses, parasites, bacteria, and fungi enter the body and cause infection in various parts of the body as a result of various reactions.

Symptoms of infection vary depending on the type of infection and the disease it causes. Fever is one of the most common symptoms of infection. In some cases, the absence of fever (eg chronic osteomyelitis) and suspicion of latent infection are conditions that make it difficult to diagnose the infection. Diagnosis of infection is usually complicated and currently available diagnostic methods show some disadvantages; thus, the treatment process could be hindered or unspecified.

Inflammation, on the other hand, is a physiological, strongly structured, defending response to an underlying infectious or non-infectious process or condition that involves cells of the immune system [2]. This condition typically causes false positive results in detecting infection lesions in imaging modalities. So, finding appropriate tracers and imaging modalities to differentiate sterile inflammation from infection and early diagnosis to control infectious diseases and provide efficient treatment is essential.

Determination of infection type and its source requires complete information, such as the patient's medical history, physical inspection, laboratory documents, and medical imaging results. The first step in infection diagnosis is microbiologic examination such as direct examination and techniques, culture, microbial identification, serodiagnosis, and antimicrobial susceptibility. Laboratory evaluation includes monitoring leukocyte count, erythrocyte sedimentation (ESR), and C-reactive protein (CRP) level and growth in blood culture. CRP, ESR, and white blood cells (WBC) have exhaustively investigated as indicators for inflammation. The infection progression is represented more accurately by CRP, since CRP levels rapidly decrease in subsiding acute infections while WBC levels may remain high due to their life span of 5–6 days [3]. One of the most important disadvantages of these markers is, that they cannot discriminate between bacterial and viral infection. This can lead to a wrong treatment procedure and unnecessary antibiotic use [4].

Medical imaging methods including radiography (x-ray), computed tomography (CT), ultrasonography, magnetic resonance imaging (MRI) and radionuclide imaging may use for the diagnosis of

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infection. Although all above-mentioned imaging techniques can spot the sicknesses' origin, nearly most of them are insufficient in discriminating between infectious and inflammation.

Radionuclide imaging modalities including Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET) tools used by specific diagnostic agents to determine and diagnose infectious and inflammation diseases are getting attention and importance in recent years. Radionuclide imaging is an early diagnosis technique, it can present increased activity within 24-48 hours after the onset of symptoms and it is preferred, especially if there is a suspicion of non-localized infection. One of the main differences between SPECT and PET imaging is the radioisotopes used. SPECT scans use radioisotopes that emit gamma rays, while PET scans use radioisotopes that emit positrons. It can be said that the sensitivity of PET is significantly higher than other imaging methods [5]. In addition, fusion camera methods, such as PET/CT SPECT/CT, and PET/MRI perform the best of both structural and pathophysiological processes. They lead to better specificities and diagnostic precisions [6]. PET/MRI camera systems might be able to bring even higher diagnostic accuracy, particularly in inflammatory situations because MRI compromises enhanced soft-tissue contrast information than CT [7].

Radioactive drugs administered for diagnostic or therapeutic purposes in nuclear medicine examinations are called radiopharmaceuticals. Radiopharmaceuticals have two important structures. The first is a radioactive element (radionuclide), which emits radioactive rays. The other is the pharmaceutical moiety to which the radionuclide is bound. In principle, radiopharmaceuticals collect in certain organs or tissues rendering to the physical, chemical, and biological properties of the pharmaceutical part to which they are attached, and organ functions can be monitored or diseases can be treated thanks to the rays emitted by the radionuclide they carry with them. In recent years, to increase the specificity of radiopharmaceuticals, targeting moieties and targeted nanoplatforms have been used as pharmaceutical parts of radiopharmaceuticals [8, 9].

Several radiopharmaceuticals have been already established based on infectious and inflammatory diseases' pathophysiology [10]. In recent years, developments in molecular biology and radiolabeling technology have led to the finding of new agents with very high specific activities, like new biomarkers, peptides, aptamers, and antibodies [11]. So, specificity must also be added to increased nuclear medicine sensitivity to distinguish both inflammatory disorder categories [12].

2. RADIOPHARMACEUTICALS USED IN THE CLINIC FOR IMAGING INFECTION

Imaging of infection by radiopharmaceuticals has a history of approximately half a century and during this time, several radiopharmaceuticals labeled with Ga-67, Tc-99m, In-111, F-18, I-131 were developed for this purpose [13]. Currently used agents for infection detection are ^{99m}Tc-methylene diphosphonate (MDP), ^{67}Ga-citrate, ^{18}F- fluorodeoxyglucose (FDG), ^{111}In-oxine- and ^{99m}Tc-hexamethyl propylene amine oxime (HMPAO)–labeled autologous leukocytes [14].

^{67}Ga-citrate is approved to be a radiopharmaceutical for imaging both acute and chronic infections, also it can be used for inflammation diagnosis. Moreover, it can be useful in osteomyelitis and fever of unknown origin (FUO) diagnosis. Gallium binds to transferrin (TF), lactoferrin (LF), ferritin, and siderophores which are iron-binding molecules. Different mechanisms have been postulated to explain the ^{67}Ga-citrate uptake in infection including leukocyte labeling, lactoferrin binding at the site of infection, and direct bacterial uptake. For the latter two mechanisms, it is assumed that the Ga-67 is available at the site of infection in either usual or increased amounts [15]. Following injection, it is assumed that approximately 90% of the circulating Ga-67 is in the plasma, nearly all bound to transferrin. Increased blood flow and vascular membrane permeability result in increased delivery and accumulation of Ga-67 at foci of infection [16]. On the other hand, it can have some drawbacks as showing uptakes in many normal tissues. Besides, slow blood clearance is another major disadvantage of this radio agent [17-19].

^{99m}Tc-MDP is also used for infections such as osteomyelitis. Uptake depends on blood flow and the rate of new bone formation. For this purpose, three-phase bone imaging is performed as dynamic imaging, perfusion, and static images of the region of interest, which is the blood pool or soft-tissue phase. Focal hyper perfusion, focal hyperemia, and focally increased bone uptake are the classic appearance of osteomyelitis. The test is sensitive and specific in normal bone but preexisting fractures, orthopedic hardware, and adjacent soft-tissue infection decrease specificity [16].

Radiolabeled leukocytes are also a method currently used clinically for imaging infections. In addition to the advantages of the method, there are also disadvantages such as the labeling process requiring a lot of processing, not being a ready-to-use radiopharmaceutical, and requiring processing with blood

components. The necessity of additional tests such as complementary marrow or bone imaging for the diagnosis of musculoskeletal system infections makes the method more costly and less convenient for patients [20]. There are different various methods for in-vitro labeling of leukocytes, ^{111}In-oxyquinoline and ^{99m}Tc-HMPAO are the two radio agents that are most used [21]. ^{111}In labeling can be stable for a reasonable period also it has a normal distribution of activity limited to the liver, spleen, and bone marrow. Its long physical half-life (67 h) provides a time for delayed imaging, and this can be very useful for mucosal infection. However, on the other side, it has a low photon flux and there is a 24-hour interval between injection and imaging, which can be a considerable drawback. ^{99m}Tc- HMPAO is another precursor used for leukocyte labeling. Tc-99 m has good imaging quality compared to other radio agents such as In-111. Another advantage is that it has a half-life of 6 hours, which is sufficient to perform imaging without exposing the patient to excessive radiation [22, 23]. However, nonspecific uptake of Tc-99m may observed in urine, bladder, gall bladder, bone marrow, and gastrointestinal system, especially in the colon [24]. So, this distribution of radioactivity leads to a false-positive diagnosis. In a total comparison view, it can be considered that ^{99m}Tclabeled leukocytes are more suitable and useful for acute inflammatory disease imaging, like inflammatory bowel disease, when, ^{111}In-labeled leukocytes are preferred for more slothful diseases as prosthetic joint infection detection. [25].

^{18}F-FDG has been used over the past years more often for infection diagnosis with PET imaging and the fact that F-FDG is taken by WBC via glucose transporter and its phosphorylating cause F-18 monitored WBC distribution in vivo [26]. Directly injected ^{18}F-FDG provides a convenient infection imaging process with high sensitivity, nevertheless, it has low specificity [27, 28]. It can show uptake in many normal organs by metabolic activity.

Based on the literatures published over the years, it can be concluded that none of the radiopharmaceuticals currently available in the clinic are excellent at imaging infection, especially in differentiating infection and inflammation. Therefore, studies are still ongoing to develop the ideal infection imaging agent.

3. RADIOPHARMACEUTICALS INVESTIGATED FOR INFECTION IMAGING

3.1 Antimicrobial Peptides

Antimicrobial peptides (AMPs), also entitled host defense peptides (HDPs), are known as an essential part of the immune response originating among all life classes. They are a varied class of naturally happening molecules formed and accepted as the first defense line by all multicellular organisms. These proteins could have an essential role in fighting against different microorganisms like viruses, bacteria, fungi, yeasts, and even cancer cells [29]. Antimicrobial peptides produced by phagocytes, epithelial cells, endothelial cells, and many other cell types are an important component of innate immunity against infections caused by a variety of pathogens. They can also be found in the body under normal conditions or can be induced in case of infection/inflammation. The common features of these peptides, which have proven microbicidal activity against various microorganisms, are their small size and cationic charge. Many antimicrobial peptides with these properties have been identified [30].

There are different types of peptides; Cationic AMPs which are commonly involved between 10 and around 50 amino acids with a complete positive charge. Folded AMPs which are classified depending on their secondary construction: α-helical; β-sheet; and extended AMPs. Prolonged AMPs which is not hold a precise design. They are distinct by a high content of particular remains, such as histidine, arginine, glycine, or tryptophan [29].

The interaction of AMPs peptides with bacterial membranes or cell walls determines the capability of AMPs to destroy bacteria. The binding of AMPs to the bacterial membrane causes non-enzymatic interference. Discrimination for precise classes is because of alterations in the membrane composition of different microbes and cell types [29].

AMPs are also considered potential targeting agents for developing radiotracers for infection detection. Accumulation of these peptides at sites of infection, besides the cytotoxicity or attraction, to host cells makes them attractive as targeting agents for radionuclide imaging of infection [31]. Moreover, radiolabeled AMPS are suggested for infection and inflammation discrimination.

To prepare the peptide-based radiotracers, it is essential to attach a radionuclide to the peptide in the radiolabeling process without changing its biological functions [32]. The process of antimicrobial labeling peptides could be quick, adequate, steady, and safe. Tc-99m which is one of the most used radionuclides in nuclear medicine imaging is also used for peptides radiolabeling. Different peptides are labeled with Tc-99m

by indirect labeling with a chelate agent or bifunctional chelating agents. On the other hand, the direct labeling technique is a more straightforward method in which the peptide is labeled in the lack of an exogenous chelator [32].

Ubiquicidin (UBI) 29–41 is a cationic, synthetic antimicrobial peptide fragment that binds preferentially with the anionic microbial cell membrane at the site of infection is one of the most studied antimicrobial peptides for infection imaging.

Studies reveal that UBI (29-41) labeled with Tc-99m and Ga-68 could distinguish sterile inflammation from infection [33-35]. Poor salt tolerance has been reported for cationic peptides. To overcome these problems, 2-acetylphenylboronic acid (2-APBA) has been incorporated into ^{99m}Tc-UBI (29-41) as a covalent probe and carried out a comparable study with ^{99m}Tc-UBI (29-41) and ^{99m}Tc-UBI (29-41)-2-APBA. Results showed that both peptide complexes are stable in serum over 16 h, and ^{99m}Tc-UBI (29-41)-2-APBA shows enhanced uptake in *S. aureus* cells as compared to ^{99m}Tc-UBI (29-41)[36].

Tc-99m labeled antimicrobial peptides can bind to both bacteria and fungi. As a result, it could be concluded that the lack of discrimination between different infection agents is a limitation of these peptides [30, 37]. Moreover, these peptides could be inadequate when the pathogens become intracellular. The bacteria are surrounded by the anti-inflammatory cells or become intracellular after the host immune cells' attack so, bacterial detection becomes more complex [38].

Gα-68 labeled RGD-peptide targeting αvβ3 integrin expression was used to quantify endothelial activation in COVID-19 patients. Based on their results increased and localized endothelial cell activation can be seen in the cardiopulmonary system in COVID-19 patients [39].

To sum up, although radiolabeled antimicrobial peptides are suggested to discriminate against infection from inflammation, they can fail too in this regard; However, they can still be promising and need more studies to develop successful agents.

3.2 Antibodies

Antibody is a large protein that plays an essential role in the immune system to detect and neutralize foreign objects like pathogenic bacteria and viruses. It can be a microbe or an infected cell for attack by other parts of the immune system. Antibodies produced by B cells (specialized white blood cells) can identify a specific molecule of the pathogen, called an antigen. When an antigen encounters a B cell, it causes the B cell to divide and clone. These cloned B cells - or plasma cells - release millions of antibodies into your bloodstream and lymph system. They mimic your immune system's natural ability to fight off pathogens. For diagnostic and therapeutic purposes, monoclonal antibodies are used. Monoclonal antibodies (mAb) discovery was back in 1975, when, Kohler and Milstein [40] established a method for selecting specific clones of cells that produced pure antibodies against a single antigen; for this purpose, animals were immunized with a target substance, as is the case for the production of polyclonal antibodies. The first antibodies used for imaging were created by immunizing an animal (usually a mouse) with human tumor cells or cell extracts and then collecting and purifying antibodies from the animal's serum or ascitic fluid [41]. These antibodies were derivatives from many B-lymphocyte clones, the polyclonal word is used to designate them. Even though radiolabeled antibodies are more commonly investigated for cancer imaging [42-45], they are also used for infection imaging [46].

In-111 or Tc-99m labeled human polyclonal immunoglobulin (HIG) has been extensively tested in many clinical studies. It has shown excellent performance in the localization of musculoskeletal infection and inflammation. In the study which was carried out in 226 patients with 232 possible foci of infection or inflammation by application of In-111 labeled to IgG, all infected areas as focal osteomyelitis, knee arthroplasties, septic arthritis, diabetic foot infections, and soft-tissue infections were distinguished (61 foci); However, ^{111}In-IgG scintigraphy could not discriminate between infectious and sterile inflammation [47]. In another study, radiolabeled human immunoglobulin (HIG) has shown good results regarding pulmonary infection-particularly in immunocompromised patients, but low sensitivity of radiolabeled HIG was observed in the diagnosis of endocarditis and vascular lesions in general, due to long-lasting high levels of circulating activity [48, 49].

In a study performed by Rubin et al., a radio iodinated murine mAb was used to recognize the sites of deep thigh infections caused by *Fisher Immunotype 1 Pseudomonas aeruginosa* to [50]. They encouraged unilateral, deep-thigh infections in rats by a shot of 2 x10^8 *Fisher Immunotype 1 P. aeruginosa* followed by an intravenous injection of radiolabeled specific mAb. The signal-to-noise percentage of the specific mAb-generated images was sustained to reinforce the distinction between explicit and non-specific mAb

produced images, which was possible at 72 hours. Based on the results, it was possible to image confined infections and concealed abscesses using organism-specific antibodies in scintigraphy [50].

Huang et al. investigated bacterial endocarditis in a rabbit model to evaluate microorganism-specific antibodies. 99m-Tc-labeled mAb which is specific to *S. aureus* was injected into rabbits, and the biodistribution was observed in both infected and control animal models. Based on this study's results, the ratio of radioactivity in the aortic valve in the surrounding heart tissue or blood pool was considerably higher in infected animals. They concluded that radiolabeled mAb could be a possibly beneficial way of detecting infected endocardial lesions [51].

Goldenberg et al. also claimed that microbe-specific radiolabeled mAb is successful in detecting infection in humans. This study observed that 99mTc-labeled mAb fragment specific for Pneumocystis carinii could localize pneumonia in human lungs after 24 h of injection [52].

It has been reported that the results obtained with the use of radiolabeled monoclonal anti-granulocyte antibodies for the diagnosis of osteomyelitis are comparable to those obtained with ^{111}In-labeled leukocytes and that the accuracy of the results obtained when combined with bone scanning is even higher than other methods used for this purpose [53].

3.3 Aptamers

Aptamers are short, single-stranded DNA (ssDNA) or single-stranded RNA (ssRNA) molecules that can selectively bind to a specific target. Generally, SELEX (Systematic Evolution of Ligands by Exponential Enrichment) method which was invented by two teams are used to generate the aptamers [54, 55]. The process relies on multiple rounds of selection and replication until high specificity and low dissociation aptamers towards the target molecule are generated. SELEX can be combined with capillary electrophoresis (CE) or surface plasmon resonance (SPR). This combination contributes to reducing the period of selection time. By using different selection strategies and modification of incubation conditions (pH, temperature, etc.), specific aptamers for different target such as single atoms, molecules, bacteria, viruses, cells and tissues can be engineered. In addition, chemical modifications of aptamers' increase their biostability in vivo. The secondary and tertiary structures of aptamers provide their binding with the target molecules [56].

Aptamers' specificities are similar to antibodies [57] but they have many advantages when compared to antibodies (Table 1)[58-60]. The main ones are smaller in size, stable for longer, reproducible without the need for experimental animals, have broader chemical labeling and modification possibilities, and are easily adaptable to many different sensor platforms. Chemical modification of aptamers increases their biostability in vivo [56]. In addition to these properties, aptamers are non-immunogenic, and their small size allows them to penetrate cells. These unique properties of aptamers make them the right choice for the development of diagnostic or therapeutic agents especially and competitive to monoclonal antibodies especially in sensor studies [61-64].

Table 1. Comparison of aptamers and antibodies [58-60].

	APTAMER	ANTIBODY
Target molecules	Any molecule or cell	Antigen
Molecular structure	Nuclide aside or peptide	Protein
Molecular size	Small (<30 Da)	Big (>75kDa)
Stability	Even if it is denatured repeatedly, it will return to its old function.	Lost its function after denaturation
Chemical function	An easy change in chemical function	Hardship in changing chemical function
Immune response	No immune response	Immune response
Affinity and specificity	High	High
Selection time	Couple of weeks	A couple of months
Cost	Low	High
Storage conditions/ storage time	Stable at room temperature, no need for freezing / (if frozen or dried) years	Easily denaturing, need for freezing / (if frozen) ~6 months

Since their discovery, aptamers have been advanced for numerous uses, including infection imaging and they have been used for detecting different kinds of infections as bacterial infections caused by

Tuberculosis [65-67], *Salmonella* [68, 69], *S. Aureus* [70], *E. coli* [71, 72]; Viral infections caused by SARS-CoV [73], Human immunodeficiency virus (HIV) [74], Hepatitis C virus [75, 76].

Nuclear imaging methods using radiolabeled aptamers for infection imaging are one of the methods with the highest potential for clinical translation. The use of aptamer as a radio agent for imaging diagnosis goes far back to 1997, in which a study was performed to isolate aptamer irreversible inhibitors of human neutrophil elastase and use it in the field of diagnostic imaging. As it was reported before it is known that enzyme elastase can bind to the surface of activated neutrophils, so, they also showed in this study that aptamer inhibitor of elastase also binds specially to activated neutrophils based on a fluorescent flow cytometry assay. In their next steps, they tested the ability of the aptamer to detect inflammation in a rat reverse passive Arthus reaction model in an in vivo test. They have reported that it is probable to apply aptamer ligands for use in diagnostic imaging, and they could offer weighty benefits over monoclonal antibodies and other reagents [77].

In a study performed by Santos *et al*., an infection caused by *S. aureus* has been imaged by Tc-99m labeled aptamers. They recommended that aptamers could be more comprehensively studied to improve specific diagnostic radiopharmaceuticals for different infection types [78]. In another study, mice were infected with *S. aureus, Candida Albicans (C. Albicans*), and Zymosan to mimic aseptic inflammation. After 24 h, radiolabeled *S. aureus-specific* aptamers were injected and biodistribution of the radiotracer was evaluated. Biodistribution results showed statistically higher uptake of *S. aureus*-specific aptamers in the *S. aureus* foci than inflammation and *C. albicans* infected areas. By this attitude, it was possible to discriminate aseptic inflammation from bacterial infection. This study's results were so promising for using radiolabeled aptamers as a radiotracer for a bacterial infection to diagnose other microorganisms and pathogens that cause infection [79].

Ferreira *et al.* performed a study about detecting bacterial infection using Tc-99m labeled peptidoglycan aptamer (Antibac1). According to biodistribution and scintigraphy imaging results, ^{99m}Tc-Antibac1 can be considered as a practicable imaging agent to detect a bacterial infection focus. Moreover, it can be a proper agent in distinguishing bacterial and fungal infections [80].

Chen *et al*. have to use radiolabeled oligomers complementary to the 16S rRNA in bacteria as bacterial infection imaging radiotracer. They concluded that a ^{99m}Tc-MORF oligomer complementary to the bacterial 16S rRNA showed binding to bacterial RNA, and radiolabeled MORF oligomers antisense to the bacterial rRNA could help imaging bacterial infection detector [81].

In another study, two radiolabeled (1→3)-β-D-glucan aptamers (coded as Seq6 and Seq30) were used as radiotracers to identify infectious foci caused by fungal or bacterial cells. Radiolabeled aptamers were injected into Swiss mice infected with *S. aureus* or *C. Albicans* (separately) in the right thigh muscle. A higher uptake of ^{99m}Tc-labeled aptamers in the infected thigh than in the left thigh muscle (non-infected) was observed. The target/non-target ratios were found as 3.17±0.22 for Seq6 and 2.66±0.10 for Seq30. Radiolabeled Seq6 and seq30 aptamers were unsuccessful in the diagnosis of *C. albicans* infection. Based on the results, radiolabeled aptamers were considered as a possible specific radio agent for *S. aureus*. The authors concluded that further studies to prove their applicability for the diagnosis of *S. aureus* and other bacterial infections could be suggested [82]. Although promising results were obtained with ^{99m}Tc-labeled aptamers in the diagnosis of infection and especially in the differentiation of infection and inflammation; still there are not many studies about using aptamers as an agent for detecting infection.

Radiolabeled aptamer studies are generally carried out with Tc-99m which is used for SPECT radioisotopes. There is a lack of examinations about aptamers radiolabeled with other radionuclides, especially with PET radioisotopes. A few studies were performed with Ga-68 and F-18 isotopes. It is well-known that PET offers many advantages such as improved image quality, better explanatory conviction, higher diagnostic accurateness, lower patient dosimetry, and shorter imaging protocols as compared to SPECT.

Based on the current studies, in a general evaluation, aptamers could be a promising in detection of infection in different ways and more investigation and studies should perform to developed aptamer-based radio agents for infection detection and discriminating infection and inflammation.

3.4 Antibiotics

Radiolabeled antibiotics can be considered a promising diagnostic method for infection detection due to the specific binding to bacteria [83]. ^{99m}Tc-ciprofloxacin is one of the first agent in the antibiotics category which was studied by Solanki et al [84]. Different clinical studies were reported for applications of ^{99m}Tc-ciprofloxacin (infection); Suspected septic arthritis or osteomyelitis (27 patients) showed a 100%

sensitivity and 37.5 specificity; Proven or suspected bone infection performed for 45 patients, showed 97.2 sensitivity 80 specificity and [85] and more recently, acute or chronic cholecystitis based on the clinical and ultrasonographic findings of 60 patients, showed a 91.7 sensitivity and 75 specify [86].

Moreover, there are other fluoroquinolone antibiotics such as ceftizoxime [87], cefoperazone [88], pefloxacin [89], lomefloxacin [90], doxycycline hyclate [91], levofloxacin [92] which were radiolabeled with Tc-99m and used for bacterial infection imaging and showed promising results [93]. However, the low binding affinity of radiolabeled antibiotics to bacteria was reported in some studies besides the risk of antibiotic-resistant microorganisms causing hesitation in using radiopharmaceuticals for imaging bacterial infections [94].

4. CONCLUSION

One of the most important issues for infection imaging is that nearly all the currently used and available radiopharmaceuticals used in clinics for infection imaging with SPECT and PET methods are insufficient, especially in the distinction between infection and inflammation. On the other hand, some newly developed radiopharmaceuticals have been shown promising result in distinguishing infection and inflammation [78, 35].

The other most important points to develop new infection imaging agent is the chelation steps of radioisotopes and ligands which is used to target to infection area. One of the issues that need to be emphasized is how radiolabeling will affect the probe entry into the bacterial cell or the mechanism of binding to the target [95].

Peptides, aptamers, antibodies, and antibiotics are considered as a successful tracer for radio imaging and diagnosis infection and inflammation despite some drawbacks for all of them. While aptamers are much smaller than antibodies, they provide greater specificity than antibodies in many cases. Moreover, they can be much cheaper and easier to modify. On the other hand, they are prone to quick degradation in biological media due to interactions with biomolecules which this could be an important disadvantage for aptamers in comparison to antibodies [95]. On the other hand, due to their low molecular weight and small size, peptides can penetrate tumors more effectively than antibodies. Also, peptides can be less toxic and exhibit low immunogenicity [14]. Finally, although antibiotics are known as chemicals that designed specifically for bacteria cells for centuries and they can be a good specific option for infection detection, radiolabeling modification of antibiotics may interfere their action mechanism could be considered as drawback [14].

Based on the literatures published over the years, it can be concluded that none of the radiopharmaceuticals currently available in the clinic are excellent at imaging infection, especially in differentiating infection and inflammation. As a result, it is believed that it is still essential to perform more studies to develop new infection-specific radiopharmaceuticals considering Bacteria-specific agents such as aptamers, and antibodies, are getting more attention for this purpose.

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REFERENCES

[1] Signore A. About inflammation and infection. EJNMMI Res. 2013; 3: 8. https://dx.doi.org/10.1186/2191-219X-3-8
[2] Oronsky B, Caroen S, Reid T. What exactly is inflammation (and what is it not?). Int J Mol Sci. 2022; 23(23): 14905. https://doi.org/10.3390/ijms232314905
[3] Heim N, Wiedemeyer V, Reich RH, Martini M. The role of C-reactive protein and white blood cell count in the prediction of length of stay in hospital and severity of odontogenic abscess. J Craniomaxillofac Surg. 2018;46(12):2220-2226. https://doi.org/10.1016/j.jcms.2018.10.013
[4] Yusa T, Tateda K, Ohara A, Miyazaki S. New possible biomarkers for diagnosis of infections and diagnostic distinction between bacterial and viral infections in children. J Infect Chemother. 2017; 23(2): 96-100. https://doi.org/10.1016/j.jiac.2016.11.002
[5] Termaat MF, Raijmakers PGHM, Scholten HJ, Bakker FC, Patka P, Haarman HJTM. The accuracy of diagnostic imaging for the assessment of chronic osteomyelitis: a systematic review and meta-analysis. J Bone Joint Surg Am. 2005; 87(11): 2464-2471.

[6] Navalkissoor S, Nowosinska E, Gnanasegaran G, Buscombe JR. Single-photon emission computed tomography–computed tomography in imaging infection. Nucl Med Commun. 2013; 34(4): 283-290. https://doi.org/10.1097/MNM.0b013e32835f0ac7
[7] Glaudemans AWJM, Quintero AM, Signore A. PET/MRI in infectious and inflammatory diseases: will it be a useful improvement? Eur J Nucl Med Mol Imaging. 2012; 39(5): 745-749. https://doi.org/10.1007/s00259-012-2060-9
[8] Erdogan S. Liposomal nanocarriers for tumor imaging. J Biomed Nanotechnol. 2009; 5(2): 141-150. https://doi.org/10.1166/jbn.2009.1016
[9] Phua VJX, Yang CT, Xia B, Yan SX, Liu J, Aw SE, He T, Ng DCE. Nanomaterial probes for nuclear imaging. Nanomaterials. 2022; 12(4): 582. https://doi.org/10.3390/nano12040582
[10] Ordonez AA, Jain SK. Pathogen-specific bacterial imaging in nuclear medicine. Semin Nucl Med. 2018; 48(2): 182-194. https://doi.org/10.1053/j.semnuclmed.2017.11.003
[11] Glaudemans AWJM, de Vries EFJ, Galli F, Dierckx RAJO, Slart RHJA, Signore A. The Use of 18F- FDG- PET/CT for diagnosis and treatment monitoring of inflammatory and infectious diseases. Clin Dev Immunol. 2013; 2013: 623036. https://doi.org/10.1155/2013/623036
[12] Corstens FH, van der Meer JW. Nuclear medicine's role in infection and inflammation. Lancet. 1999; 354(9180): 765-770. https://doi.org/10.1016/S0140-6736(99)06070-5
[13] Riddhi PD, Patel PM, Patel NM. A review on radiopharmaceuti- cals and radiochemical method in analysis. Int J Pharm Biol Arch. 2011; 2(4): 1062-1067.
[14] Salmanoglu E, Kim S, Thakur ML. Currently available radiopharmaceuticals for imaging infection and the holy grail. Semin Nucl Med; 2018: 48(2): 86-99. https://doi.org/10.1053/j.semnuclmed.2017.10.003
[15] Hoffer P. Gallium: mechanisms. J Nucl Med. 1980;21(3): 282-285.
[16] Palestro CJ. Radionuclide imaging of musculoskeletal infection: A review. J Nucl Med. 2016; 57(9): 1406-1412. https://doi.org/10.2967/jnumed.115.157297
[17] Connolly CM, Donohoe KJ. Nuclear medicine imaging of infection. Semin Roentgenol. 2017; 52(2): 114-119. https://doi.org/10.1053/j.ro.2016.07.001
[18] Das SS, Hall AV, Wareham DW, Britton KE. Infection imaging with radiopharmaceuticals in the 21st century. Braz Arch Biol Technol. 2002; 45: 25-37. https://doi.org/10.1590/S1516-89132002000500005
[19] Goldsmith SJ, Vallabhajosula S. Clinically proven radiopharmaceuticals for infection imaging: mechanisms and applications. Semin Nucl Med; 2009: 39(1): 2-10. https://doi.org/10.1053/j.semnuclmed.2008.08.002
[20] Love C, Palestro CJ. Radionuclide imaging of infection. J Nucl Med Technol. 2004; 32(2): 47-57.
[21] Karesh SM, Henkin RE. Preparation of 111In leukocytes after hemolytic removal of erythrocytes. Int J Rad Appl Instrum Part B. 1987; 14(1): 79-80. https://doi.org/10.1016/0883-2897(87)90166-8
[22] Robins PD, Salazar I, Forstrom LA, Mullan BP, Hung JC. Biodistribution and radiation dosimetry of stabilized 99mTc-exametazime-labeled leukocytes in normal subjects. J Nucl Med. 2000; 41(5): 934-940.
[23] Weldon MJ, Joseph AE, French A, Saverymuttu SH, Maxwell JD. Comparison of 99m technetium hexamethylpropylene-amine oxime labelled leucocyte with 111-indium tropolonate labelled granulocyte scanning and ultrasound in the diagnosis of intra-abdominal abscess. Gut. 1995; 37(4): 557-564. https://doi.org/10.1136/gut.37.4.557
[24] Kakkar D, Tiwari AK, Singh H, Mishra AK. Past and present scenario of imaging infection and inflammation: A nuclear medicine perspective. Mol Imaging. 2012;11(4): 09–337 309. https://doi.org/10.2310/7290.2011.00051
[25] Palestro CJ, Torres M. Radionuclide imaging of nonosseous infection. Q J Nucl Med. 1999; 43(1): 46-60.
[26] Autio A, Jalkanen S, Roivainen A. Nuclear imaging of inflammation: homing-associated molecules as targets. EJNMMI Res. 2013; 3: 1-7. https://doi.org/10.1186/2191-219X-3-1
[27] Jamar F, Buscombe J, Chiti A, Christian PE, Delbeke D, Donohoe KJ, Israel O, Martin-Comin J, Signore A. EANM/SNMMI guideline for 18F-FDG use in inflammation and infection. J Nucl Med. 2013; 54(4): 647-658. https://doi.org/10.2967/jnumed.112.112524
[28] van der Bruggen W, Bleeker-Rovers CP, Boerman OC, Gotthardt M, Oyen WJ. PET and SPECT in osteomyelitis and prosthetic bone and joint infections: a systematic review. Semin Nucl Med; 2010: 40(1): 3-15. https://doi.org/10.1053/j.semnuclmed.2009.08.005
[29] Izadpanah A, Gallo RL. Antimicrobial peptides. J Am Acad Dermatol. 2005; 52(3): 381-390. https://doi.org/10.1016/j.jaad.2004.08.026
[30] Akhtar MS, Imran MB, Nadeem MA, Shahid A. Antimicrobial peptides as infection imaging agents: better than radiolabeled antibiotics. Int J Pept. 2012; 965238. https://doi.org/10.1155/2012/965238
[31] Okarvi SM. Peptide- based radiopharmaceuticals: Future tools for diagnostic imaging of cancers and other diseases. Med Res Rev. 2004; 24(3): 357-397. https://doi.org/10.1002/med.20002
[32] Okarvi S. Recent developments in 99Tcm-labelled peptide-based radiopharmaceuticals: an overview. Nucl Med Commun. 1999; 20(12): 1093-1112. https://dx.doi.org/10.1097/00006231-199912000-00002
[33] Akhtar MS, Qaisar A, Irfanullah J, Iqbal J, Khan B, Jehangir M, Nadeem MA, Khan MA, Afzal MS, Ul-Haq I, Imran MB. Antimicrobial peptide 99mTc-ubiquicidin 29–41 as human infection-imaging agent: clinical trial. J Nucl Med. 2005; 46(4): 567-573.

[34] Jiang Y, Zhang J. Current status of and perspectives on radiolabelled Ubiquicidin 29-41 derivatives for bacterial infection imaging. Mini-Rev Med Chem. 2023; 23(15): 1500-1506. https://dx.doi.org/10.2174/1389557523666230131100654
[35] Welling MM, Paulusma-Annema A, Balter HS, Pauwels EK, Nibbering PH. Technetium-99m labelled antimicrobial peptides discriminate between bacterial infections and sterile inflammations. Eur J Nucl Med. 2000; 27(3): 292-301. https://doi.org/10.1007/s002590050036
[36] Mitra JB, Chatterjee S, Kumar A, Bandyopadhyay A, Mukherjee A. Integrating a covalent probe with ubiquicidin fragment enables effective bacterial infection imaging. RSC Med Chem. 2022; 13(10): 1239-1245. https://doi.org/10.1039/D2MD00190J
[37] Akhtar MS, Iqbal J, Khan MA, Irfanullah J, Jehangir M, Khan B, Ul-Haq I, Muhammad G, Nadeem MA, Afzal MS, Imran MB. 99mTc-labeled antimicrobial peptide ubiquicidin (29-41) accumulates less in *Escherichia coli* infection than in *Staphlococcus aureus* infection. J Nucl Med. 2004;45(5):849-56.
[38] Singh A, Verma J, Bhatnager A, Sen S. Tc-99m Isoniazid: A specific agent for diagnosis of tuberculosis. World J Nuc Med. 2003;2(4):292-305.
[39] van Genugten EAJ, van Lith TJ, van den Heuvel FMA, van Steenis JL, Ten Heggeler RM, Brink M, Rodwell L, Meijer FJA, Lobeek D, Have WHT, van de Veerdonk FL, Netea MG, Prokop M, Nijveldt R, Tuladhar AM, Aarntzen EHJG. Gallium-68 labelled RGD PET/CT imaging of endothelial activation in COVID-19 patients. Sci Rep. 2023; 13(1): 11507. https://doi.org/10.1038/s41598-023-37390-9.
[40] Köhler G, Milstein C. Continuous cultures of fused cells secreting antibody of predefined specificity. Nature. 1975; 256(5517): 495-497.https://doi.org/10.1038/256495a0
[41] Harrison KA, Tempero MA. Diagnostic use of radiolabeled antibodies for cancer. Oncology (Williston Park). 1995; 9(7): 625-631.
[42] Palesto CJ. Radiolabeled Antibodies for Diagnostic Imaging. In: Dübel S, Reichert JM (Eds). Handbook of therapeutic antibodies: Wiley- VCH Verlag GmbH & Co., 2014, pp. 2123-2142. https://doi.org/10.1002/9783527682423.ch76
[43] Sarcan ET, Özer Y. Monoclonal antibodies and immuno-PET imaging: An overview. FABAD J Pharm Sci. 2023; 48(1): 165-182. https://doi.org/10.55262/fabadeczacilik.1172020
[44] Erdogan S, Roby A, Sawant R, Hurley J, Torchilin VP. Gadolinium-loaded polychelating polymer-containing cancer cell-specific immunoliposomes. J Liposome Res. 2006; 16(1): 45-55. https://doi.org/10.1080/08982100500528784
[45] Silindir-Gunay M, Karpuz M, Ozturk N, Ozer AY, Erdogan S, Tuncel M. Radiolabeled, folate-conjugated liposomes as tumor imaging agents: formulation and in vitro evaluation. J Drug Deliv Sci Technol. 2019; 50: 321-328. https://doi.org/10.1016/j.jddst.2019.02.003
[46] Bensimon C, Redshaw R. Antibody Radiolabeling. In: Shire SJ, Gombotz W, Bechtold-Peters K, Andya J (Eds). Current Trends in Monoclonal Antibody Development and Manufacturing. Springer, New York, 2010, pp. 323-344. https://doi.org/10.1007/978-0-387-76643-0
[47] Nijhof MW, Oyen WJ, van Kampen A, Claessens RA, van der Meer JW, Corstens FH. Evaluation of infections of the locomotor system with indium-111-labeled human IgG scintigraphy. J Nucl Med. 1997; 38(8): 1300-1305.
[48] Buscombe JR, Oyen WJG, Grant A, Claessens RAMJ, van der Meer JWM, Corstens FHM, Ell PJ, Miller RF. Indium-111-labeled polyclonal human immunoglobulin: identifying focal infection in patients positive for human immunodeficiency virus. J Nucl Med. 1993; 34(10): 1621-1625.
[49] Oyen WJ, Claessens RA, Raemaekers JM, de Pauw BE, van der Meer JW, Corstens FH. Diagnosing infection in febrile granulocytopenic patients with indium-111-labeled human immunoglobulin G. J Clin Oncol. 1992; 10(1): 61-68. https://dx.doi.org/10.1200/JCO.1992.10.1.61
[50] Rubin RH, Young LS, Hansen WP, Nedelman M, Wilkinson R, Nelles MJ, Callahan R, Khaw BA, Strausset HW. Specific and nonspecific imaging of localized Fisher immunotype 1 *Pseudomonas aeruginosa* infection with radiolabeled monoclonal antibody. J Nucl Med. 1988; 29(5): 651-656.
[51] Huang JT, Raiszadeh M, Sakimura I, Montgomerie JZ, Harwig JF. Detection of bacterial endocarditis with technetium-99m-labeled antistaphylococcal antibody. J Nucl Med. 1980; 21(8): 783-786.
[52] Goldenberg DM, Sharkey RM, Udem S, Vagg R, Levine GM, Conte P, Swayne LC, Hansen HJ, Cunniff D, Anton J, Linke MJ, Smulian AG, Walzer PD. Immunoscintigraphy of *Pneumocystis carinii* pneumonia in AIDS patients. J Nucl Med. 1994; 35(6): 1028-1034.
[53] Palestro CJ, Kipper SL, Weiland FL, Love C, Tomas MB. Osteomyelitis: diagnosis with 99mTc-labeled antigranulocyte antibodies compared with diagnosis with 111In-labeled leukocytes—initial experience. Radiology. 2002; 223(3): 758-764. https://doi.org/10.1148/radiol.2233011072
[54] Ellington AD, Szostak JW. In vitro selection of RNA molecules that bind specific ligands. Nature. 1990; 346(6287): 818-822. https://doi.org/10.1038/346818a0
[55] Tuerk C, Gold L. Systematic evolution of ligands by exponential enrichment: RNA ligands to bacteriophage T4 DNA polymerase. Science. 1990; 249(4968): 505-510. https://doi.org/10.1126/science.2200121
[56] Wandtke T, Woźniak J, Kopiński P. Aptamers in diagnostics and treatment of viral infections. Viruses. 2015; 7(2): 751-780. https://doi.org/10.3390/v7020751
[57] Keefe AD, Pai S, Ellington A. Aptamers as therapeutics. Nature Reviews Drug Discovery. 2010; 9(7): 537-550. https://doi.org/10.1038/nrd3141

[58] Hidding J. Master Thesis, A therapeutic battle: Antibodies vs. Aptamers. University of Groningen, Nanosci Master Progr, 2017; NS109 Research Paper.
[59] Lopez-Silva C, Surapaneni A, Coresh J, Reiser J, Parikh CR, Obeid W, Grams ME, Chen TK. Comparison of aptamer-based and antibody-based assays for protein quantification in chronic kidney disease. Clin J Am Soc Nephrol. 2022; 17(3): 350-360. https://dx.doi.org/10.2215/CJN.11700921
[60] Thiviyanathan V, Gorenstein DG. Aptamers and the next generation of diagnostic reagents. Proteomics Clin Appl. 2012; 6(11-12): 563-573. https://dx.doi.org/10.1002/prca.201200042
[61] Ferreira IM, de Souza Lacerda CM, de Faria LS, Corrêa CR, de Andrade ASR. Selection of peptidoglycan-specific aptamers for bacterial cells identification. Appl Biochem Biotechnol. 2014; 174: 2548-2556. https://doi.org/10.1007/s12010-014-1206-6
[62] Banerjee J, Nilsen-Hamilton M. Aptamers: Multifunctional molecules for biomedical research. J Mol Med (Berl). 2013; 91: 1333-1342. https://doi.org/10.1007/s00109-013-1085-2
[63] Barbas AS, Mi J, Clary BM, White RR. Aptamer applications for targeted cancer therapy. Future Oncol. 2010; 6(7): 1117-1126. https://doi.org/10.2217/fon.10.67
[64] Ilgu M, Fazlioglu R, Ozturk M, Ozsurekci Y, Nilsen-Hamilton M. Aptamers for diagnostics with applications for infectious diseases. Recent Adv Anal Chem. 2019:1-32. https://doi.org/10.5772/intechopen.84867
[65] Lavania S, Das R, Dhiman A, Myneedu VP, Verma A, Singh N, Sharma TK, Tyagi JS. Aptamer-Based TB Antigen tests for the rapid diagnosis of pulmonary tuberculosis: Potential utility in screening for tuberculosis. ACS Infect Dis. 2018; 4(12): 1718-1726. https://doi.org/10.1021/acsinfecdis.8b00201.
[66] Sypabekova M, Jolly P, Estrela P, Kanayeva D. Electrochemical aptasensor using optimized surface chemistry for the detection of *Mycobacterium tuberculosis* secreted protein MPT64 in human serum. Biosens Bioelectron. 2019; 123: 141-1451. https://doi.org/10.1016/j.bios.2018.07.053
[67] Chen Y, Liu X, Guo S, Cao J, Zhou J, Zuo J, Bai L. A sandwich-type electrochemical aptasensor for *Mycobacterium tuberculosis* MPT64 antigen detection using C(60)NPs decorated N-CNTs/GO nanocomposite coupled with conductive PEI-functionalized metal-organic framework. Biomaterials. 2019; 216: 119253. https://doi.org/10.1016/j.biomaterials.2019.119253
[68] Ye H, Duan N, Gu H, Wang H, Wang Z. Fluorometric determination of lipopolysaccharides via changes of the graphene oxide-enhanced fluorescence polarization caused by truncated aptamers. Mikrochim Acta. 2019; 186(3): 173. https://doi.org/10.1007/s00604-019-3261-8
[69] Li L, Li Q, Liao Z, Sun Y, Cheng Q, Song Y, Song E, Tan W. Magnetism-resolved separation and fluorescence quantification for near-simultaneous detection of multiple pathogens. Anal Chem. 2018; 90(15): 9621-9628. https://doi.org/10.1021/acs.analchem.8b02572
[70] Cai R, Yin F, Zhang Z, Tian Y, Zhou N. Functional chimera aptamer and molecular beacon based fluorescent detection of *Staphylococcus aureus* with strand displacement-target recycling amplification. Anal Chim Acta. 2019; 1075: 128-136. https://doi.org/10.1016/j.aca.2019.05.014
[71] Wei X, Zhou W, Sanjay ST, Zhang J, Jin Q, Xu F, Dominguez DC, Li X. Multiplexed Instrument-Free Bar-Chart SpinChip integrated with nanoparticle-mediated magnetic aptasensors for visual quantitative detection of multiple pathogens. Anal Chem. 2018; 90(16): 9888-9896. https://dx.doi.org/10.1021/acs.analchem.8b02055
[72] Zhang Y, Zhu L, He P, Zi F, Hu X, Wang Q. Sensitive assay of *Escherichia coli* in food samples by microchip capillary electrophoresis based on specific aptamer binding strategy. Talanta. 2019; 197: 284-290. https://dx.doi.org/10.1016/j.talanta.2019.01.040
[73] Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Sİ HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020; 579(7798): 270-273. https://dx.doi.org/10.1038/s41586-020-2012-7
[74] Caglayan MO, Üstündağ Z. Spectrophotometric ellipsometry based Tat-protein RNA-aptasensor for HIV-1 diagnosis. Spectrochim Acta A Mol Biomol Spectrosc. 2020; 227: 117748. https://dx.doi.org/10.1016/j.saa.2019.117748
[75] Ghanbari K, Roushani M, Azadbakht A. Ultra-sensitive aptasensor based on a GQD nanocomposite for detection of hepatitis C virus core antigen. Anal Biochem. 2017; 534: 64-69. https://dx.doi.org/10.1016/j.ab.2017.07.016
[76] Li X, Yin C, Wu Y, Zhang Z, Jiang D, Xiao D, Fang X, Zhou C. Plasmonic nanoplatform for point-of-care testing trace HCV core protein. Biosens Bioelectron. 2020; 147: 111488. https://dx.doi.org/10.1016/j.bios.2019.111488
[77] Charlton J, Sennello J, Smith D. In vivo imaging of inflammation using an aptamer inhibitor of human neutrophil elastase. Chem Biol. 1997; 4(11): 809-816. https://doi.org/10.1016/S1074-5521(97)90114-9
[78] Dos Santos SR, de Sousa Lacerda CM, Ferreira IM, Dos Santos SR, de Barros ALB, Fernandes SO, Cardoso VN, de Andrade ASR. Scintigraphic imaging of *Staphylococcus aureus* infection using 99mTc radiolabeled aptamers. Appl Radiat Isot. 2017; 128: 22-27. https://doi.org/10.1016/j.apradiso.2017.06.043
[79] Dos Santos SR, Corrêa CR, de Barros ALB, Serakides R, Fernandes SO, Cardoso VN, de Andrade ASR. Identification of *Staphylococcus aureus* infection by aptamers directly radiolabeled with technetium-99m. Nucl Med Biol. 2015; 42(3): 292-298. https://doi.org/10.1016/j.nucmedbio.2014.12.002

[80] Ferreira IM. de Souza Lacerda CM, Santos SR, Fernandes SO, de Barros AB, Cardoso VN, Andrade ASR: Evaluation of anti-peptidoglycan aptamers labeled with Technetium-99m for in vivo bacterial infection identification. International Nuclear Atlantic Conference, INAC-2017, Belo Horizonte, Brazil, 2017.

[81] Chen X, Yan GY. Novel human lncRNA–disease association inference based on lncRNA expression profiles. Bioinformatics. 2013; 29(20): 2617-2624. https://doi.org/10.1093/bioinformatics/btt426

[82] de Sousa Lacerda CM, Ferreira IM, Dos Santos SR, de Barros ALB, Fernandes SO, Cardoso VN, de Andrade ASR. (1→ 3)-β-D-glucan aptamers labeled with technetium-99 m: Biodistribution and imaging in experimental models of bacterial and fungal infection. Nucl Med Biol. 2017; 46: 19-24. https://doi.org/10.1016/j.nucmedbio.2016.11.008

[83] Singh B, Mittal B, Bhattacharya A, Aggarwal A, Nagi O, Singh A. Technetium-99m ciprofloxacin imaging in the diagnosis of postsurgical bony infection and evaluation of the response to antibiotic therapy: A case report. J Orthop Surg (Hong Kong). 2005; 13(2): 190-194. https://doi.org/10.1177/230949900501300217

[84] Solanki KK, Bomanji J, Siraj Q, Small M, Britton KE. Tc-99m "Infecton"—a new class of radiopharmaceutical for imaging infection. J Nucl Med. 1993; 34(Suppl): 119.

[85] Malamitsi J, Giamarellou H, Kanellakopoulou K, Dounis E, Grecka V, Christakopoulos J, Koratzanis G, Antoniadou A, Panoutsopoulos G, Batsakis C, Proukakis C. Infecton: a 99mTc-ciprofloxacin radiopharmaceutical for the detection of bone infection. Clin Microbiol Infect. 2003;9(2):101-109.https://doi.org/10.1046/j.1469-0691.2003.00506.x

[86] Choe YM, Choe W, Lee KY, Ahn SI, Kim K, Cho YU, Choi SK, Hur YS, Kim SJ, Hong KC, Shin SH, Kim KR, Woo ZH. Tc-99m ciprofloxacin imaging in acute cholecystitis. World J Gastroenterol: 2007; 13(23): 3249-3252.

[87] Barreto VG, Iglesias F, Roca M, Tubau F, Martín-Comín J. Labelling of ceftizoxime with 99mTc. Rev Esp Med Nucl. 2000; 19(7): 479-483.

[88] Motaleb IM, Attalah K. Synthesis and biological distribution of 99m Tc–norfloxacin complex, a novel agent for detecting sites of infection. J Radioanal Nucl Chem. 2010; 285(3): 431-436. https://doi.org/10.1007/s10967-010-0607-4

[89] El-Ghany EA, El-Kolaly T, Amine AM, El-Sayed AS, Abdel-Gelil F. Synthesis of 99m Tc-pefloxacin: A new targeting agent for infectious foci. J Radioanal Nucl Chem. 2005; 266(1): 131-139. https://doi.org/10.1007/s10967-005-0881-8

[90] Motaleb MA. Preparation and biodistribution of 99mTc-lomefloxacin and 99mTc-ofloxacin complexes. J Radioanal Nucl Chem. 2007; 272(1): 95-99. https://doi.org/10.1007/s10967-006-6786-3

[91] İlem- Özdemir D, Asikoglu M, Ozkilic H, Yilmaz F, Hosgor- Limoncu M, Ayhan S. 99mTc- Doxycycline hyclate: A new radiolabeled antibiotic for bacterial infection imaging. J Labelled Comp Radiopharm. 2014; 57(1): 36-41. https://doi.org/10.1002/jlcr.3135

[92] Silindir-Gunay M, Ozer AY. 99mTc-radiolabeled Levofloxacin and micelles as infection and inflammation imaging agents. J Drug Deliv Sci Technol. 2020; 56: 101571. https://doi.org/10.1016/j.jddst.2020.101571

[93] Gouws AC, Kruger HG, Gheysens O, Zeevaart JR, Govender T, Naicker T, Ebenhan T. Antibiotic- Derived Radiotracers for Positron Emission Tomography: Nuclear or "Unclear" Infection Imaging? Angew Chem Int Ed Engl. 2022; 134(45): e202204955. https://doi.org/10.1002/anie.202204955

[94] Welling MM, Visentin R, Feitsma HIJ, Lupetti A, Pauwels EKJ, Nibbering PH. Infection detection in mice using 99mTc-labeled HYNIC and N2S2 chelate conjugated to the antimicrobial peptide UBI 29-41. Nucl Med Biol. 2004; 31(4): 503-509. https://doi.org/10.1016/j.nucmedbio.2003.11.009

[95] Northrup JD, Mach RH, Sellmyer MA. Radiochemical approaches to imaging bacterial infections: Intracellular versus extracellular targets. Int J Mol Sci. 2019; 20(22): 5808. https://doi.org/10.3390/ijms20225808