Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 12 [11] October 2023 : 418-424

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD

REVIEW ARTICLE **OPEN ACCESS**

Evolving Approaches in Musculoskeletal Infection: Insights and Future Directions in Nuclear Medicine

Rajesh Aithagoni[1], Krupavaram.B[2*], Rabia Arafa[3], Pravallika Padyala[4], Chayakanta Behera[5], Jochhana Rani Bhuyan[6], G Venkata Nagaraju[7]

[1] Avalon University School of Medicine, world trade Centre , Willemstad, Curaçao
[2] KPJ Healthcare University, School of Pharmacy, Kota Seriemas, 71800 Nilai, Negeri Sembilan, Malaysia
[3] Windsor University School of Medicine, Saint Kitts
[4] Baylor University,1311 S 5th St, Waco, TX 76706, 1 Bear Place 70232,Waco,Texas
[5] Asst. Professor, Department of Pharmaceutics, College of Pharmaceutical Sciences, Mohuda, Berhampr, Odisha , Pin - 760002, India
[6] Asst. Professor, Department of Pharmaceutics, College of Pharmaceutical Sciences, Mohuda, Berhampr, Odisha, Pin - 760002, India
[7] Department of Pharmacy Practice, Hindu College of Pharmacy, Amaravati Road, Guntur, Andhra Pradesh, India
***Corresponding Author's** Email: ucn.krupa@kpju.edu.my

ABSTRACT

Nuclear medicine has become essential in diagnosing and treating musculoskeletal infections. Radionuclide tests are valuable for diagnosing prosthetic joint infections, osteomyelitis, or spondylodiscitis. The choice of imaging method depends on parameters like the affected area, potential involvement beyond bones, or previous bone/joint problems. This review discusses traditional radionuclide imaging and recent fusion imaging advancements for diagnosing musculoskeletal infections. It also looks into how radionuclide scans track treatment responses and current patterns in their utilization. This update will interest orthopedic surgeons, rheumatologists, internists, radiologists, rehabilitation physicians, and others in musculoskeletal pathology. Musculoskeletal infections pose significant challenges in diagnosis and treatment, often necessitating a multidisciplinary approach for effective management. Nuclear medicine techniques have emerged as valuable tools in the diagnostic armamentarium, offering insights into the pathophysiology and aiding in the timely and accurate detection of infections. This review provides an overview of evolving approaches in the nuclear medicine landscape for musculoskeletal infections, highlighting recent advancements, challenges, and future directions.
Keywords: *Musculoskeletal infection, scintigraphy, FDG-PET/TC, osteomyelitis, spondylodiscitis, nuclear medicine, periprosthetic infections, septic arthritis.*

Received 21.07.2023 Revised 11.08.2023 Accepted 23.09.2023

INTRODUCTION

Musculoskeletal infections include a range of circumstances, from superficial skin infections to deep-seated osteomyelitis and also prosthetic joint infections. Prompt and accurate diagnosis is important for initiating proper treatment and preventing long-term complications [1]. While assessing musculoskeletal infections, traditional imaging modalities like radiography, magnetic resonance imaging (MRI), and computed tomography (CT) are essential.; however, they may lack sensitivity and specificity in certain clinical scenarios. Nuclear medicine techniques offer complementary information, enabling the detection of infection at an early stage and guiding therapeutic decision-making [2].

Nuclear medicine (NM) examinations are crucial for diagnosing and characterizing infections and inflammation in rheumatology. They are particularly important for identifying and evaluating musculoskeletal (MSK) infections, which includes infectious spondylodiscitis (SD), prosthetic joint infections (PJI) and osteomyelitis (OM) [3].

NM tests includes administering a radionuclide intravenously, emitting detectable radiation for assessment using a gamma camera. This method allows the identification of atypical bone metabolism, presenting as areas with increased radionuclide uptake. Such scans provide metabolic and functional insights, often

revealing early disease stages before morphological changes occur. The appropriate investigation should be designed exclusively to each and every patient and clinical situation, because not a single radionuclide agent is efficient universally for all bone sites. [4].

Although traditional radionuclide imaging techniques like the gallium scan, radiolabeled leukocyte scan, and three-phase bone scan has long been utilized to diagnose MSK infection, questions regarding their diagnostic limits have arisen [5]. To tackle this, combined imaging scans like positron emission tomography with CT (PET/CT) accompanied by computed tomography (SPECT/CT) and single-photon emission computed tomography are being developed. These approaches are essential for biasing between soft tissue as well as bone infections because they provide morphological data. This review thoroughly examines the current applications of nuclear medicine (NM) and its potential future uses in managing musculoskeletal (MSK) infections [6].

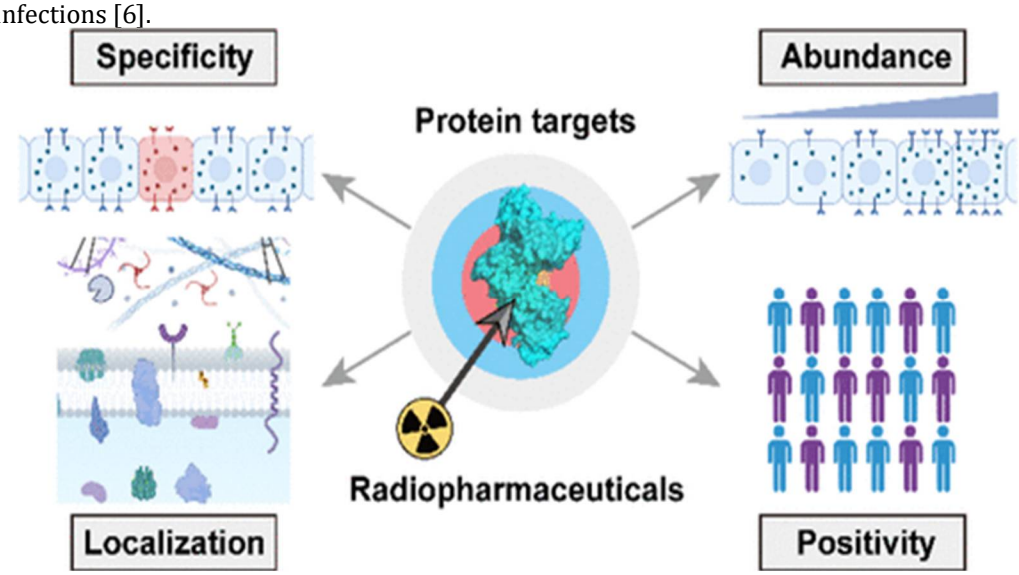

Figure 1. Role of Radiopharmaceuticals in diagnosis

Role of Nuclear Medicine in Musculoskeletal Infections

Radiolabeled Leukocyte Scintigraphy

Radiolabeled leukocyte scintigraphy, using agents such as technetium-99m (Tc-99m) hexamethylpropylene amine oxime (HMPAO) or indium-111 (In-111) oxine, has been widely utilized for the detection of musculoskeletal infections [7]. By exploiting the phagocytic activity of leukocytes, this technique facilitates the localization of inflammatory foci with high sensitivity, allowing for differentiating infection from sterile inflammation. Radiolabeled leukocyte scintigraphy exhibits high sensitivity (approximately 90%) and specificity (approximately 85-95%) for diagnosing musculoskeletal infections, with the added advantage of whole-body imaging capability [8]. Despite its utility, limitations such as the need for leukocyte isolation and radiotracer preparation, as well as potential false-positive results in cases of sterile inflammation, have been reported [9].

Gallium-67 Citrate Scintigraphy

Gallium-67 citrate scintigraphy has been beneficial in the diagnosis of persistent osteomyelitis as well as infected prosthetic joints. Accumulation of gallium-67 within infectious sites reflects increased vascular permeability and inflammatory activity, aiding in the localization and characterization of musculoskeletal infections. Gallium-67, a radiotracer with a strong affinity for inflammatory cells, concentrates in regions of infection due to enhanced vascular permeability along with the presence of activated macrophages. [10]. While gallium scintigraphy demonstrates good sensitivity for detecting musculoskeletal infections, ranging from 70% to 90%, its specificity may be compromised by non-specific uptake in areas of trauma, neoplasia, or granulomatous inflammation. Additionally, delayed imaging at 48-72 hours post-injection may be necessary to differentiate between infection and non-specific uptake [11].

18F-FDG PET/CT

18F-fluorodeoxyglucose (FDG) positron emission tomography in conjunction with computed tomography (PET/CT) has been developed as an effective imaging method for evaluating musculoskeletal infections. [12]. FDG is a glucose analog that accumulates within metabolically active tissues, including inflammatory lesions and infected areas. PET/CT provides high-resolution anatomical localization along with metabolic information, enhancing the sensitivity as well as specificity of infection detection. Meta-analyses have

demonstrated pooled sensitivity and also specificity values of around 90% and 80-85%, respectively, for 18F-FDG PET/CT in detecting musculoskeletal infections. Moreover, PET/CT enables the diagnosis of occult infections, evaluation of treatment response, and localization of infectious foci in challenging anatomical locations [13].

Novel Radiotracers and Imaging Approaches

Ongoing research efforts focus on the development of novel radiotracers targeting specific molecular pathways associated with infection, such as bacterial cell wall synthesis, metabolic activity, or immune response markers [14]. For instance, radiolabeled antibiotics, peptides, or antibodies have been investigated for their potential to selectively bind to bacterial targets or host inflammatory markers, enabling the precise localization of infectious foci. Furthermore, advanced imaging techniques, such as PET/MRI, offer the combined strengths of molecular imaging with superior soft tissue contrast, facilitating comprehensive evaluation and accurate localization of musculoskeletal infections [15].

Potential Advancements in Bone Infection Treatment: Novel Radiopharmaceuticals

As fusion imaging becomes more prevalent in clinical settings, there's a growing focus on innovating SPECT or PET radiopharmaceuticals and enhancing SPECT or PET/CT systems. These advancements aim to produce higher-resolution images at a quicker pace compared to conventional methods.

Gallium-68-Citrate (^{68}Ga)

^{68}Ga in the form of ^{68}Ga -citrate proves to be more effective than ^{67}Ga-citrate in diagnosing bone infections. Its shorter physical half-life (68 minutes) allows for higher tracer doses and reduced patient dosimetry compared to ^{67}Ga. Imaging conducted a few hours after administering the radiopharmaceutical yields superior image quality compared to ^{67}Ga. However, both ^{68}Ga and ^{67}Ga exhibit uptake via nonspecific mechanisms in inflammation, trauma, malignancies, and infections [16]. While the significance of ^{68}Ga-citrate imaging in musculoskeletal infections (MSK) requires further exploration, limited data suggest promising results. For example, in an investigation conducted by Nanni et al., ^{68}Ga-citrate revealed a level of specificity of 76% and sensitivity of 100% in identifying spinal osteomyelitis. A research carried out by Tseng et al. included 34 patients, suspected with prosthetic hip/knee joint infections who received ^{68}Ga-citrate PET/CT along with sequential 18F-FDG PET/CT imaging [17]. The research disclosed that ^{68}Ga-citrate had a higher specificity and also similar sensitivity to 18F-FDG PET/CT in detecting infections. Furthermore, it efficiently differentiated across infected as well as sterile inflammation. [18, 19].

Sodium Fluoride (18F-NaF)

Recently, the use of sodium fluoride (18F-NaF) in combination with PET/CT has been reinstated. Because osseous blood flow and bone remodeling have an impact on 18F-NaF absorption, it is an extremely sensitive technique for examining bone remodeling brought on by infection or inflammation. Since 18F-NaF is a radiotracer that predominantly measures cortical osteoblastic function, it has the important attribute of being independent of marrow activity [20]. Because of its better target-to-background ratio, sensitivity, as well as spatial resolution, 18F-NaF PET/CT may therefore be a useful substitute for triphasic 99mTc scans [21]. Nevertheless, disadvantages include increased expense, marginally higher radiation dose, and maybe higher false-positive rates because of greater absorption at degenerative change sites.

A research was carried out with 23 patients with probable condition of post-surgical bone infection, who received dual-phase F-18-NaF bone PET/CT and found a sensitivity of 92.9%, specificity of 100.0%, and accuracy of 95.7% [22]. Furthermore, a systematic review was documented with data pertaining to dynamic or multi-sequential 18F-NaF PET used in diagnosis and differentiation of septic as well as aseptic loosening in hip prostheses. The outcome of the study was found to have a diagnostic sensitivity along with specificity of 97.04% and 88.11% respectively, for identifying periprosthetic joint infection (PJI). In accordance with this, a current clinical trial (NCT04842071) is looking into the safety as well as efficacy of 18F-NaF PET/CT as an alternative to triphasic 99mTc scans [23].

Technetium-Labelled Interleukin-8 (IL-8)

Technetium-labelled Interleukin-8 (IL-8) is a radiopharmaceutical used in nuclear medicine for imaging purposes, particularly in the context of inflammation detection. Interleukin-8 (IL-8) is a chemokine, a type of signaling molecule involved in the immune response, particularly in the recruitment of white blood cells to sites of inflammation.

In the context of medical imaging, technetium (Tc) is a radioactive isotope commonly used in radiopharmaceuticals due to its favorable nuclear properties and low radiation exposure risk to patients. By labelling IL-8 with technetium, it becomes possible to track and visualize the distribution of IL-8 in the body using imaging techniques such as single-photon emission computed tomography (SPECT) or gamma

camera imaging. This technique allows clinicians to non-invasively assess areas of inflammation or infection in the body. Technetium-labelled IL-8 can be particularly useful in diagnosing conditions such as osteomyelitis, inflammatory bowel disease, and certain types of infections [24].
The process typically involves isolating and purifying IL-8, conjugating it with a technetium radioisotope, and then administering it to the patient intravenously. The labelled IL-8 then binds to specific receptors in inflamed tissue, allowing for the visualization and quantification of inflammation through imaging scans. In rabbit models of osteomyelitis (OM), IL-8 tagged with 99mTc could detect OM lesions. The initial clinical study of 99mTc-IL-8 scintigraphy revealed great tracer tolerance, which enabled the detection of different infections in patients at the 4-hour point post-injection [25-27].

Radiolabeled Antibiotics
Numerous researchers have developed innovative tracers utilizing antibiotic compounds to enhance the specificity of bone infection detection, with a significant portion of these tracers labeled with 99m-Tc for SPECT imaging. Among the examples of 99mTc-labeled drugs are ciprofloxacin, enrofloxacin, norfloxacin, cephazolin, ceftizoxime, ertapenem, isoniazid, and metronidazole. However, the emergence of resistance poses a substantial difficulty in antibiotic therapy for infections and imaging with 99mTc-labeled medicines [28–29].
The most widely explored radiolabeled antibiotic in musculoskeletal (MSK) infections is 99mTc-ciprofloxacin, which has shown good sensitivity and specificity in identifying MSK infections in published trials. However, excessive bone neoformation, aseptic osteoarticular disorders, and primary bone malignancies should be avoided since they may result in false-positive results [30]. Certain investigations have shown that 99mTc-ciprofloxacin is more effective than bone/gallium imaging and labeled leukocyte bone scans in the treatment of suspected periprosthetic joint infection. It may also be useful for tracking antibiotic responses. Despite exciting concepts and good preliminary results, the current state of development of these tracers makes them premature for immediate routine clinical application [31].
One drawback of labeling antibiotics with radiometals such as 99m-Tc is the potential to affect the antibiotic's ability to penetrate bacteria or interfere with its binding to intracellular targets [32]. To address this limitation, researchers might explore the use of PET-compatible "organic" radionuclides like 13N or 11C, as well as 18F-based compounds like 18F-linezolid or 11C-isoniazid/rifampicin/pyrazinamide, which have been investigated in animal studies. These alternatives, characterized by their relatively small atomic radius, are anticipated to minimally impact the molecular structure of the antibiotic [33].
Remarkably, [11C]-trimethoprim ([11C] TMP) has been trialed in human subjects utilizing PET/CT. Lee et al. employed [11C]-TMP PET/CT in patients afflicted with infections caused by both trimethoprim-sensitive and trimethoprim-resistant organisms, revealing localized radiotracer uptake at sites of infectious lesions [34]. Another notable PET tracer based on antibiotics is 18F-fluoropropyl-trimethoprim ([18F] F-TMP), an analogue of the bacterial dihydrofolate reductase inhibitor. PET studies have demonstrated its ability to differentiate between infection, chemical inflammation, and malignancies in rodent models. An ongoing clinical investigation (NCT04263792) is evaluating the biodistribution and kinetics of [18F] F-TMP PET/CT in human subjects [35–38].

CHALLENGES AND LIMITATIONS
Despite the advantages offered by nuclear medicine techniques in diagnosing musculoskeletal infections, several challenges and limitations persist. Interpretation of imaging findings requires expertise To distinguish infection from other causes of inflammation. accurately. False-positive results may occur in cases of sterile inflammation, recent surgery, or trauma, necessitating correlation with clinical and microbiological data [39]. Furthermore, concerns regarding radiation exposure, tracer availability, and cost-effectiveness may impact the widespread adoption of nuclear medicine modalities in routine clinical practice. Standardization of imaging protocols, optimization of radiotracer production, and validation of quantitative imaging biomarkers are essential steps toward addressing these challenges and enhancing the clinical utility of nuclear medicine imaging in musculoskeletal infections [40].

FUTURE DIRECTIONS
Future directions in nuclear medicine for musculoskeletal infections encompass several areas of research and development aimed at overcoming existing limitations and expanding diagnostic capabilities. This includes the refinement of imaging protocols to improve diagnostic accuracy and reduce radiation exposure, particularly in vulnerable patient populations such as children and pregnant women. Moreover, efforts to develop targeted molecular imaging strategies, utilizing radiotracers specific to bacterial virulence factors or host immune responses, hold promise for enhancing the specificity and sensitivity of

infection detection. Integration of artificial intelligence algorithms for image analysis and interpretation represents another frontier in nuclear medicine research, enabling automated detection of infectious foci, quantitative assessment of disease burden, and prediction of treatment response. Furthermore, collaborative initiatives between orthopedic surgeons, nuclear medicine physicians, radiologists, and infectious disease specialists are essential for the successful translation of these evolving approaches into clinical practice.

CONCLUSION

Nuclear medicine techniques play a vital role in the diagnosis as well as management of musculoskeletal infections, offering valuable insights into the pathophysiology and aiding in early detection. Evolving approaches, including radiolabeled leukocyte scintigraphy, 18F-FDG PET/CT, gallium-67 citrate scintigraphy, and novel radiotracers, hold promise for improving diagnostic accuracy and guiding therapeutic decision-making. Despite challenges and limitations, ongoing advancements in imaging technology, radiotracer development, and artificial intelligence integration offer exciting opportunities for enhancing the precision, efficiency, and accessibility of nuclear medicine imaging in musculoskeletal infections. Multidisciplinary collaboration and concerted research efforts are essential for realizing the full potential of these innovative approaches and improving patient outcomes in the future.

These advancements not only enhance diagnostic accuracy but also aid in the early detection of infections, allowing for timely intervention and improved patient outcomes. Moreover, nuclear medicine techniques offer the advantage of being non-invasive, reducing patient discomfort and the need for invasive procedures.

Looking ahead, further research and development in nuclear medicine are expected to drive innovations in imaging modalities, including the incorporation of novel radiotracers and imaging technologies. Additionally, the integration of nuclear medicine with other diagnostic modalities and therapeutic approaches holds promise for personalized and targeted management strategies for musculoskeletal infections.

Overall, the evolving landscape of nuclear medicine in musculoskeletal infection underscores its pivotal role in advancing patient care and underscores the importance of continued collaboration between clinicians, researchers, and industry stakeholders to unlock new insights and improve clinical outcomes in this challenging domain.

REFERENCES

1. J. Sciuk. (2004). Scintigraphic techniques for the diagnosis of infectious disease of the musculoskeletal system. Semin. Musculoskelet.Radiol. 8:205–213.
2. C. Love, S. E. Marwin, & C. J. Palestro. (2003). Nuclear medicine and the infected joint replacement. Seminars in Nuclear Medicine, 33(1): 47-64. DOI: 10.1053/snuc.2003.127292.
3. J. Maamari, A.J. Tande, F. Diehn, D.B.G. Tai, & E.F. Berbari. (2022). Diagnosis of vertebral osteomyelitis. J. Bone Jt. Infect. 27:23–32.
4. F. Gemmel, H. Van den Wyngaert, C. Love, M. M. Welling, P. Gemmel, & C. J. Palestro, (2013). Prosthetic joint infections: radionuclide state-of-the-art imaging. European Journal of Nuclear Medicine and Molecular Imaging, 40(6): 907-912. DOI: 10.1007/s00259-012-2345-3.
5. B. Vanquickenborne, A. Maes, J. Nuyts, F. Van Acker, J. Stuyck, M. Mulier, & L. Mortelmans. (2003). The value of (18) FDG-PET for the detection of infected hip prosthesis. European Journal of Nuclear Medicine and Molecular Imaging, 30(5): 705-715. DOI: 10.1007/s00259-003-1135-6.
6. F. Gemmel, P. C. Rijk, J. M. Collins, T. Parlevliet, K. D. M. Stumpe, & C. J. Palestro. (2001). Expanding role of 18F-fluoro-D-deoxyglucose PET and PET/CT in spinal infections. European Journal of Nuclear Medicine and Molecular Imaging, 28(9): 1209-1220. DOI: 10.1007/s002590100543.
7. W. Zimmerli, A. Trampuz, & P. E. Ochsner. (2004). Prosthetic-joint infections. New England Journal of Medicine, 351(16): 1645-1654. DOI: [10.1056/NEJMra040181] (https://doi.org/10.1056/NEJMra040181)
8. E. F. Berbari, S. S. Kanj, T. J. Kowalski, R. O. Darouiche, A. F. Widmer, S. K. Schmitt, & Osmon, D. R. (2015). 2015 Infectious Diseases Society of America (IDSA) clinical practice guidelines for the diagnosis and treatment of native vertebral osteomyelitis in adults. Clinical Infectious Diseases, 61(6):e26-e46. DOI: [10.1093/cid/civ482].
9. D. P. Lew, & F. A. Waldvogel. (2004). Osteomyelitis. New England Journal of Medicine, 351(16): 1654-1665. DOI: [10.1056/NEJMra030831].
10. D. R. Osmon, E. F. Berbari, A. R. Berendt, D. Lew, W. Zimmerli, & J. M. Steckelberg. (2013). Infectious Diseases Society of America. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. Clinical infectious diseases, 56(1):e1-e25. DOI: [10.1093/cid/cis803]
11. P. Tattevin, A. C. Cremieux, P. Pottier, & C. Carbon. (1999). Prosthetic joint infection: when can prosthesis salvage be considered? Clinical infectious diseases, 29(2):292-295. DOI: [10.1086/520193]

12. H. Morales. (2018). Infectious spondylitis mimics: Mechanisms of disease and imaging findings. Semin. Ultrasound CT MR. 39: 587–604.
13. L. Bernard, A. Dinh, I. Ghout, D. Simo, V. Zeller, & B. Issartel. (2014). Groupe des Infections Ostéo-Articulaires du Service de Santé des Armées (GIOA). Antibiotic treatment for 6 weeks versus 12 weeks in patients with pyogenic vertebral osteomyelitis: an open-label, non-inferiority, randomised, controlled trial. The Lancet, 385(9971):875-882. DOI: [10.1016/S0140-6736(14)60472-7]
14. P. C. Matthews, A. R. Berendt, M. A. McNally & I. Byren. (2009). Diagnosis and management of prosthetic joint infection. The Journal of antimicrobial chemotherapy, 64(suppl_1):i29-i37. DOI: [10.1093/jac/dkp260]
15. L. Grammatico-Guillon, S. Baron, S. Gettner, A. I. Lecuyer, C. Gaborit, P. Rosset, & E. Rusch. (2012). Bone and joint infections in hospitalized patients in France, 2008: clinical and economic outcomes. The Journal of Infection, 65(6):556-564. DOI: [10.1016/j.jinf.2012.08.008](https://doi.org/10.1016/j.jinf.2012.08.008)
16. P. Sendi, F. Banderet, P. Graber, W. Zimmerli, M. Clauss, & M. Berli. (2011). Predicting implant retention in patients with acute Staphylococcus aureus prosthetic joint infections: a cohort study. BMC Infectious Diseases, 11(1):1-7. DOI: [10.1186/1471-2334-11-254]
17. E. Senneville, D. Joulie, L. Legout, M. Valette, H. Dezeque, E. Beltrand, & Y. Yazdanpanah. (2008). Outcome and predictors of treatment failure in total hip/knee prosthetic joint infections due to Staphylococcus aureus. Clinical Infectious Diseases, 47(1):70-75. DOI: [10.1086/588292]
18. A. Gasbarrini, L. Boriani, C. Salvadori, & F. Gherlinzoni. (2012). Concomitant deep spinal infection and epidural abscesses in intravenous drug abusers: is anterior approach the best treatment? European Spine Journal, 21(3):529-536. DOI: [10.1007/s00586-011-2078-7]
19. J. L. Brusch. (2009). Clinical manifestations and diagnosis of acute haematogenous osteomyelitis in children and adolescents. Clinical infectious diseases, 21(1):212-225.
20. D. T. Tsukayama, R. Estrada, & R. B. Gustilo. (1996). Management of infection after total hip arthroplasty: a protocol for treatment. The Journal of Bone & Joint Surgery, 78(4):511-523. DOI: [10.2106/00004623-199604000-00004]
21. S. Kurtz, K. Ong, E. Lau, F. Mowat, & M. Halpern. (2007). Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. The Journal of Bone & Joint Surgery, 89(4):780-785. DOI: [10.2106/00004623-200704000-00012]
22. J.P. Pijl, P.H. Nienhuis, T.C. Kwee, A.W.J.M. Glaudemans, R.H.J.A. Slart, & L.C. Gormsen, (2021). Limitations and Pitfalls of FDG-PET/CT in Infection and Inflammation. Semin. Nucl. Med. 51: 633–645.
23. D.J.W. Hulsen, C. Mitea, J.J. Arts, D. Loeffen, & J. Geurts.(2022). Diagnostic value of hybrid FDG-PET/MR imaging of chronic osteomyelitis. Eur. J. Hybrid. Imaging. 6:15.
24. I. Seong, E. Kong & I. Jeon. (2021). Clinical and Radiological Features Predicting Intervertebral Autofusion after Successful Antibiotic Therapy in Pyogenic Vertebral Osteomyelitis. Diagnostics.11:1349.
25. V.S. Krishnaraju, H. Singh, R. Kumar, S. Sharma, B.R. Mittal, & A. Bhattacharya. (2021). Infection imaging using [18F]FDG-labelled white blood cell positron emission tomography-computed tomography. Br. J. Radiol. 94:20201204.
26. D. Manda, P. Thakral, I. Sen, S.S. Das, V. Cb, & D. Malik. (2022). Incremental Value of 18 F-FDG-Labeled Leukocytes PET/CT Over 18 F-FDG PET/CT Scan in the Detection of Occult Infection. Clin. Nucl. Med. 47:e574–e581.
27. S.A.R. Naqvi, & K. Drlica.(2017). Fluoroquinolones as imaging agents for bacterial infection. Dalton Trans. 46:14452–14460.
28. Z. Yapar, M. Kibar, A.F. Yapar, E. Togrul, U. Kayaselcuk, & Y. Sarpel. (2001). The efficacy of technetium-99m ciprofloxacin (Infecton) imaging in suspected orthopaedic infection: A comparison with sequential bone/gallium imaging. Eur. J. Nucl. Med. 28:822–830.
29. J.L. Pierce, M.T. Perry, D.E. Wessell, L. Lenchik, S. Ahlawat, J.C. Baker, J. Banks, J.T. Caracciolo, K.C. DeGeorge, & J. Demertzis, et al. (2022). ACR Appropriateness CriteriaRSuspected Osteomyelitis, Septic Arthritis, or Soft Tissue Infection (Excluding Spine and Diabetic Foot): 2022 Update. J. Am. Coll. Radiol. 19:S473–S487.
30. E. Righi, A. Carnelutti, D. Muser, F. Di Gregorio, B. Cadeo, G. Melchioretto, M. Merelli, A. Alavi, & M. Bassetti. (2020). Incremental value of FDG-PET/CT to monitor treatment response in infectious spondylodiscitis. Skeletal Radiol. 49:903–912.
31. L. Jodal, P. Afzelius, A.K.O. Alstrup, & S.B. Jensen. (2021). Radiotracers for Bone Marrow Infection Imaging. Molecules. 26:3159.
32. P. Afzelius, P.M.H. Heegaard, S.B. Jensen, A.K.O. Alstrup, H.C. Schonheyder, A. Eek, O. Boerman, & O.L. Nielsen. (2020). [99mTc]-labelled interleukin-8 as a diagnostic tool compared to [18F]FDG and CT in an experimental porcine osteomyelitis model. Am. J.Nucl. Med. Mol. Imaging. 10:32–46.
33. S.A.R Naqvi. (2022). 99m Tc-labeled antibiotics for infection diagnosis: Mechanism, action, and progress. Chem. Biol. Drug Des. 99:56–74.
34. Y. Wang, Y. Li, L. Han, J. Wang, C. Zhang, E. Qi, D. Zhang, X. Zhang, Y. Huan, & J. Tian. (2022). 18F-FDG and 68 Ga-FAPI PET/CT for the evaluation of periprosthetic joint infection and aseptic loosening in rabbit models. BMC Musculoskelet. Disord. 23:592.
35. Q. Pan, H. Yang, Z. Zhou, M. Li, X. Jiang, F. Li, Y. Luo, & M. Li. (2024). [68Ga]Ga-FAPI-04 PET/CT may be a predictor for early treatment response in rheumatoid arthritis. EJNMMI Res. 14:2.
36. C. Qin, Y. Song, X. Liu, Y. Gai, Q. Liu, W. Ruan, F. Liu, F. Hu, & X. (2022). Lan. Increased uptake of 68Ga-DOTA-FAPI-04 in bones and joints: Metastases and beyond. Eur. J. Nucl. Med. Mol. Imaging. 49:709–720.

37. S. Liu, M. Feng, T. Qiao, H. Cai, K. Xu, X. Yu, W. Jiang, Z. Lv, Y. Wang, & D. Li. (2022). Deep Learning for the Automatic Diagnosis and Analysis of Bone Metastasis on Bone Scintigrams. Cancer Manag. Res. 14:51–65.
38. E. Dadachova, & D.E.N. Rangel. (2022). Highlights of the Latest Developments in Radiopharmaceuticals for Infection Imaging and Future Perspectives. Front. Med. 9:819702.
39. I.K. Lee, D.A. Jacome, J.K. Cho, V. Tu, A.J. Young, T. Dominguez, J.D. Northrup, J.M. Etersque, H.S. Lee, A. Ruff, & et al. (2022). Imaging sensitive and drug-resistant bacterial infection with [11C]-trimethoprim. J. Clin. Investig. 132:e156679.
40. K.M.G. Mokoala, H. Ndlovu, I. Lawal, & M.M. Sathekge. (2023). PET/CT and SPECT/CT for Infection in Joints and Bones: An Overview and Future Directions. Semin. Nucl. Med., in press.

CITATION OF THIS ARTICLE

Rajesh A, Krupavaram.B, Rabia A, Pravallika P, Chayakanta B, Jochhana R B, G Venkata Nagaraju. Evolving Approaches in Musculoskeletal Infection: Insights and Future Directions in Nuclear Medicine. Bull. Env. Pharmacol. Life Sci., Vol 12 [11] October 2023: 418-424