

The authors are correct that there is much more information to be gleaned from our data and we appreciate their input. We chose to present the most clinically relevant information to the readership of *Journal of Arthroplasty* and to stimulate a discussion about the interaction between instruments used in TKA surgery, patient anatomy and surgical accuracy. Nonetheless, we hope this dataset can be helpful in designing more in depth anatomic studies of arthritic knees.

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Comment on: “Diagnosis of Periprosthetic Joint Infection: The Role of Nuclear Medicine May Be Overestimated” by Claudio Diaz-Ledezma, Courtney Lamberton, Paul Lichtstein and Javad Parvizi



To the Editor:

We read with interest the article by Diaz-Ledezma et al entitled “Diagnosis of Periprosthetic Joint Infection: The Role of Nuclear Medicine May Be Overestimated” recently published in *The Journal of Arthroplasty* [1].

We agree with the authors that an accurate and efficient diagnosis of prosthetic joint infection (PJI) is a challenge and of invaluable importance for the patient and for the whole medical community, since PJI leads to a high morbidity and a significant increase in financial costs [2]. The aims of the Infection and Inflammation Committee of the European Association of Nuclear Medicine (EANM) are to develop clear interpretation criteria for the various existing nuclear medicine techniques, to teach each centre how to correctly acquire and interpret the images and to develop, in

collaboration with other societies, common diagnostic flow charts to state clearly to the clinician what we can offer and at which time point in the diagnostic work-up of the patient.

The article by Diaz-Ledezma et al raised some concerns to us, since some interpretations they made need to be clarified.

First of all, the authors state in the first paragraph that two workgroups “could not find concrete evidence in support of using bone scan or nuclear imaging for diagnosis of PJI”. This sentence is misleading since most of the published systematic reviews agree on the role of nuclear medicine, and particularly with the high diagnostic accuracy of scintigraphy with radiolabelled white blood cells (WBC) [3–5]. Also a large workgroup with both imaging specialists and orthopaedic surgeons conducted a critical appraisal of studies reporting the accuracy of nuclear imaging for diagnosis of PJI by using the QUADAS-2 tool and recommended, based on their findings, that there is substantial evidence regarding the effectiveness of nuclear imaging in diagnosing PJI, although it should be limited to select cases [6].

Later on, they state that “there is a dire need for further evidence to support the use of this otherwise invasive and relatively expensive diagnostic modality”. We would like to emphasise that nuclear medicine procedures are non-invasive and non-expensive as compared to other diagnostic modalities.

Furthermore, authors included in their analysis studies performed with ⁶⁷Gallium-citrate, radiolabelled white blood cells (WBC) and radiolabelled anti-granulocyte antibodies. These methods cannot be pooled together since they have different diagnostic accuracies and different indications.

In general, there are two strategies for using nuclear medicine techniques in PJI: (1) Use the bone scan with radiolabelled diphosphonates to see if there is an increased osteoblastic activity. It is universally accepted that a normal bone scan can be considered as a strong evidence against the presence of an infection. However, a positive bone scan cannot distinguish infections from other bone inflammatory conditions and therefore a positive bone scan is aspecific. To further clarify when this technique should be used, one has to keep in mind that a bone scan may be positive for at least 2 years after hip prosthesis placement and 5 years after knee prosthesis placement due to physiological bone re-modelling after implantation. During these intervals, the bone scan should not be used as a first imaging technique. (2) Use radiopharmaceuticals that are able to image infection. The first nuclear imaging modality of choice is based on the use of radiolabelled autologous WBC. When using the correct acquisition and interpretation criteria this technique has a high diagnostic accuracy (>90%). The scintigraphy with radiolabelled anti-granulocyte antibodies can be used as an alternative to WBC-scintigraphy in centres that are not able to label the autologous white blood cells. ⁶⁷Gallium scintigraphy – one of the search criteria in this study! – is an obsolete technique that is outperformed by other techniques and should not be used anymore for diagnosing PJI. Another imaging technique that is frequently used in PJI is ¹⁸F-fluorodeoxyglucose for positron emission tomography (FDG-PET) which is not mentioned at all by the authors.

To our regret, the studies included in the paper of Diaz-Ledezma et al show a huge variety of radiopharmaceuticals but not always the correct ones used in modern nuclear medicine.

Another striking concern is the timeframe for inclusion of the studies (January 1, 2004 till July 31, 2012). On the contrary, in the discussion a paper from 2014 is discussed that states that nuclear medicine studies should be abandoned as a first diagnostic approach for PJI. In the last years there has been a huge development in nuclear medicine techniques. Not only better camera systems were developed, they were also hybrid systems, which made it possible to perform 3D images of the patient and to exactly localise the pathological uptake of any radiopharmaceutical (combining pathophysiology with anatomy, the so called SPECT-CT) leading to high diagnostic accuracy. Furthermore, several studies have recently been published for WBC scintigraphy, focusing on how to correctly acquire the images and how to correctly interpret the scans.

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Alberto Signore is chair of the Inflammation and Infection Committee of the European Association of Nuclear Medicine (EANM) and Andor W.J.M. Glaudemans, Paola A. Erba, Elena Lazzeri are members of this Committee. Paul Jutte is member of the European Bone and Joint Infection Society (EBJIS) and Nicola Petrosillo is member of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID). Authors jointly contribute to the preparation of shared guidelines for diagnosis of prosthetic joint infections.

When following these strategies, diagnostic accuracy is >93% [7,8]. Most of the papers analysed by Diaz-Ledezma et al have not used a correct imaging protocol or standardised interpretation criteria. SPECT/CT should be performed for a more detailed localisation of WBC accumulation, particularly for differentiating between osteomyelitis and soft tissue infection.

We agree that it is very important to compare the results of the imaging techniques with correct reference standards like given by the IDSA and AAOS [9,10]. This should be pathology and/or microbiology, or at least a thorough clinical follow-up time of at least six months. Of course, scans have to be performed at a predefined time point in the diagnostic work-up of the patient and at the same time point as other diagnostic procedures to reliably compare the results of the different techniques with each other. We don't know exactly if and how the use of steroids and/or antibiotics influences the uptake of e.g. the labelled white blood cells. To overcome these limitations, we (not only nuclear medicine specialists but also surgeons and the whole medical community) are in need of prospective randomised trials to finally get evidence based data for the use of the different techniques.

In our opinion and supported by most recently published evidence, when using the correct acquisition protocols, the correct interpretation protocols and hybrid imaging techniques, there is an added value of nuclear medicine techniques, which are not only highly convenient for the patient (non-invasive, one-stop-shop principle) but could even lead to cost effectiveness by telling the clinician exactly when to perform invasive techniques and when not.

Last year, an expert panel of nuclear medicine specialists, radiologists, orthopaedic surgeons and infectious disease specialists proposed a diagnostic flow chart about when to use which technique at which time point in patients with a suspicion of PJI [11]. This flow chart should be the basis for further studies. Indeed, members of the Infection and Inflammation Committee of the EANM are right now, in collaboration with delegates from the European Society of Radiology (ESR), the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the European Bone and Joint Infection Society (EBJIS) working on joint guidelines for the diagnosis of PJI. We welcome the American Societies to join us in future efforts to commonly make correct statements of how and when to use nuclear medicine techniques.

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In Reply



We welcome the interest of our esteemed colleagues in our published article entitled "Diagnosis of Periprosthetic Joint Infection: The Role of Nuclear Medicine May Be Overestimated."

The lack of uniformity in the diagnosis of periprosthetic joint infection (PJI) [1] and the variability in reporting the outcome of treatment of this disease [2] continue to be an issue in the field of orthopedics. The Infection and Inflammation Committee of the European Association of Nuclear Medicine should be congratulated for their effort to decrease variability in performing bone scan imaging and interpreting the results of this test. It can certainly be beneficial to patients, clinicians, and researchers.

The authors raise some specific points regarding our publication that we would like to address. Our interpretation of "concrete evidence to support the use of any given diagnostic tool for PJI" not only depends on the results published as a percentage of accuracy, but the relevance with which that evidence is weighted when compared to other tools. That fact represents the strongest manifestation of a tangible clinical value. In consequence, "concrete evidence" becomes, from our standpoint, a synonym of support for clinical usefulness. Neither the American Academy of Orthopaedic Surgeons guidelines [3] nor the International Consensus Meeting (ICM) on PJI [4] recommends the use of nuclear medicine studies for the diagnosis of PJI. A large percentage of the delegates (93%) at the ICM felt that there was no direct role for bone scans in the diagnosis of PJI. This most probably reflects the experience of the majority of experts in the field of orthopedics and what is reflected in the literature, as detected by our study, in that bone scans usually provide inconclusive data that cannot be directly employed in reaching or refuting the diagnosis of PJI. Glaudemans et al also stated "Most of the papers analyzed by Diaz-Ledezma et al. have not used a correct imaging protocol or standardized interpretation criteria." This is indeed a very sobering statement as it implies that studies in the field of nuclear medicine regarding PJI have suffered from serious shortfalls, and this leaves one to wonder why these studies ever found their way into the literature.

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