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Response to Wouthuyzen-Bakker et al regarding: "Labeled white blood cell/bone marrow single-photon emission computed tomography with computed tomography fails in diagnosing chronic periprosthetic shoulder joint infection"

In reply:

We thank Wouthuyzen-Bakker et al for the opportunity to respond to comments on our recently published article "Labeled white blood cell/bone marrow single-photon emission computed tomography with computed tomography fails in diagnosing chronic periprosthetic shoulder joint infection."[3] We appreciate their interest in our article that investigates the diagnostic accuracy of indium-labeled white blood cell/bone marrow single-photon emission computed tomography with computed tomography (WBC/BM SPECT/CT) in diagnosing chronic periprosthetic shoulder joint infections (PJIs).

It is pointed out that the Infection and Inflammation Committee of the European Association of Nuclear Medicine (EANM) recently published an evidence-based consensus document on a diagnostic strategy and a flow chart of the recommended use of nuclear medicine procedures. A thorough review of the available literature made by a collaboration of medical experts in diagnosing PJI is welcomed in a field of somewhat heterogeneous diagnostic strategies. The consensus document from EANM was unfortunately not published at the time of initiating of our study nor at the time of submitting and revising of the article, and as such could not be discussed in our article. When we write that "no exact diagnostic approach has yet been established despite extensive research in biomarkers, radionuclide imaging, and the use of consensus infectious criteria such as developed by the Musculoskeletal Infection Society (MSIS) or the American Academy of Orthopaedic Surgeons (AAOS)," this statement points in general toward both the order in which to perform different investigations and especially how to define PJI, regardless of diagnostic modality used. The sentence does not exclusively pertain to nuclear imaging in PJI, as it could be interpreted by the appearance of the quote in the response. As recently debated at the international consensus meeting on PJI in Philadelphia (www.icmphilly.com), with the presence of members of our group, no gold standard exists and many aspects of the definition and classification of PJI need to be further addressed.[1,4]

Regarding labeled WBC scans for investigating skeletal infections, we acknowledge that planar images at multiple time points and no use of SPECT/CT are the current recommendation from EANM. However, the consensus document states that the use of SPECT/CT increases the ability to assess the extent of infection, and is recommended in cases with positive WBC scans.[5] Furthermore, given the development in scanner technology and availability, a more widespread use of SPECT/CT as a standard first-line procedure can be expected.

The main objections to our method are (1) the use of 111-indium (^{111}In) as a radiotracer for labeling WBC and (2) the timing of imaging acquisition.

Concerning the choice of radioisotope, it is correct that 99-tecnetium (^{99m}Tc) has physical, economic, and radiation properties that could favor its use compared with ^{111}In. Based on this, ^{99m}Tc is proposed as the first choice in WBC scintigraphy by the EANM.[2] However, the EANM guideline states: "As ^{111}In-WBC scintigraphy is preferable in low-grade infection, delayed and late imaging is usually sufficient and is not impaired by elution of the radiolabel from WBC."[4] Because the expected infection in our study cohort was low-grade infection caused by *Cutibacterium acnes*, the use of ^{111}In seems justified. We are well aware of differences in radiation using ^{111}In routinely instead of ^{99m}Tc. The increased radiation exposure is limited to 3 mSv using the ^{111}In protocol (8-10 mSv) compared with the ^{99m}Tc-HMPAO-WBC protocol (7 mSv). Although minimizing radiation dosage to patients is always a concern, we do not feel that such a discrete difference is enough to rule out the use of ^{111}In, particularly given the mean age of our study cohort (64 years) and the typical clinical patient population.

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Concerning the acquisition of WBC scintigraphies at multiple time points (delayed and late), we fully acknowledge the comprehensive studies performed over the last decade.[1,4,6] Using both visual and semiquantitative methods, acquisition of dual time point WBC scintigraphies appears to allow for a robust discrimination between inflammation and infection based on the tissue radioactivity curve (increasing in infection and decreasing in inflammation). This approach thus minimizes the risk of *false-positive* studies resulting in fewer subsequent unnecessary septic revisions, a huge clinical benefit. However, it is not our opinion that acquisition of dual time point WBC scintigraphies in a similar fashion may reduce the fraction of *false-negative* studies, because the delayed scintigraphy is essentially rendered redundant if the late image is negative. As stated clearly by the authors in their papers, all studies with negative late images are to be considered negative for infection, because a negative late study can only be the consequence of either unchanged or decreasing tissue radioactivity. False-negative late images were indeed the problem in our study, where no uptake was detected in 9 infected prostheses that were explanted; hence the poor sensitivity and diagnostic accuracy were reported in our paper. We fully acknowledge that acquisition of delayed images would have been helpful had we observed a significant fraction of false-positive studies. This, however, was not the case because the 2 scintigraphies with increased periprosthetic radioactivity at the late scan turned out to be true positive for infection. In summary, we believe that the low sensitivity of our study is more likely a result of low-grade infection, which does not evoke a sufficient leucocyte response to elicit a positive scan, rather than our choice of isotope or a wrong imaging protocol.

We appreciate the encouragement to continue our research and will heed the advice to do dual time point leukocyte imaging in the future.

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