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Molecular Imaging of Bacteria in Patients is an Attractive Fata Morgana, Not a Realistic Option

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TO THE EDITOR: We read with great interest the review article entitled, "Metabolic Imaging of Infection" by Lawal et al. *(1)*. This communication and several others over the years have advocated imaging bacteria as a potential for further exploration *(2-5)*. Indeed, it would be wonderful if PET could tell if there was an ongoing bacterial infection in the body, how aggressive it was, and whether antibiotics were effective or not. Interesting studies on bacterial imaging with candidate probes were made in bacterial cultures or with bacterial inoculates in small animals (2-5). The researchers knew exactly where to look and what they were looking for, and some of them made optimistic predictions about the clinical significance of their laboratory results. We feel an obligation to contest too optimistic or misleading statements, because experimental circumstances differ vastly from the conditions in the human body, where similarly high concentrations of pathogenic bacteria are rarely seen in the same spot and therefore seldom visible by PET.

We have in recent editorial commentaries expressed our views on the limitations of PET imaging in several settings including detection and characterization of bacterial infections (*6-8*). Even with modern digital detectors, time of flight acquisition and iterative reconstruction, the spatial or the volume resolution with PET has difficulty in getting better than 5 mm or 65 mm^3, respectively. Thus, PET remains a gross imaging modality that faces substantial challenges in visualizing structures at the cellular and subcellular levels, particularly when the intended tracer is not taken up by a mass of cells or other structures with a volume of considerable size. In order to visualize biological phenomena in both normal and disease states, a large volume of cells (or other targets) needs to be

clumped together in a volume that is larger than several mm^3 or perhaps one cm^3 to be detectable by PET imaging, and the degree of tracer uptake in such volumes has to substantially exceed that of the background activity by at least 2-3 times to attain an adequate contrast (*9*). As a result, attempts to detect and visualize targets that are smaller than a few mm^3 and with lower levels of activity will fail based on these known physical limitations of PET and may lead to conduct of studies that generate uncertain results. With a medium-sized spherical bacteria of a diameter of 2 μm equal to a volume of about 4.2 μm^3, it would require approximately 3.5×10^9 of these bacteria to create a target volume of about 65 mm^3 corresponding to a 5 diameter spherical lesion barely detectable by PET. This enormous concentration of bacteria is about the maximal obtainable in the microbiology lab and will hardly ever be present in the body. Bacteria in the tissues lie more scattered and are almost instantaneously attacked by the immune system and macrophages that ingest and remove them, and, thus, bacterial concentrates in the body that are visible with bacterial PET tracers is more a rarity than a commonplace event.

Several tracers are very specific by targeting characteristics of living bacteria *(3,4)* or being labeled antimicrobial agents *(2,5)*, however, the value of specificity depends on the purpose of imaging. Ironically, a very high specificity may imply a low clinical usefulness because we cannot image all patients with a large panel of tracers, like one for staphylococci, another for pneumococci, and a third for E. coli. Specific tracers may be the crux for the future of PET, but very specific tracers are not always as representative of what we want to detect or as specific as initially assumed. For instance, abnormal uptake of amyloid probes for the study of Alzheimer's disease is frequently seen in patients without this disease, and anti-PSMA tracers appear to target other cancers than prostate cancer *(10)*. Therefore, it is gratifying that some of the authors of bacteria imaging express caveats. Neumann et al. highlight the competition from the huge numbers of non-pathogenic bacteria in the body *(2)*, while Sellmeyer et al. modestly state that “noninvasive identification of sites of bacterial

infection could increase our understanding of the natural history of bacterial infection in patients" and "be used to support clinical decision making" *(3)*.

The problems with PET imaging of bacteria mimic the challenges of PET in general. We call for more specific tracers, but at the same time they should not always be too specific. PET may have few limits, since in principle most biologic molecules can be labeled, but we have to consider when it is worth the effort and the cost. Like it or not, until further FDG remains the most important clinical tracer for imaging inflammation in the body, whether it is sterile or bacterial.

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