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

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. To visualize biologic 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 1 cm^3 to be detectable by PET imaging, and the degree of tracer uptake in such volumes must 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 studies that generate uncertain results. With a medium-sized spheric 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 spheric lesion barely detectable by PET. This enormous concentration of bacteria is about the maximal obtainable in the microbiology laboratory 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 are 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, such as 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 disease is frequently seen in patients without this disease, and anti–prostate-specific membrane antigen tracers appear to target cancers other 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 nonpathogenic bacteria in the body (*2*), whereas 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, for the time being ^{18}F-FDG remains the most important clinical tracer for imaging inflammation in the body, whether it is sterile or bacterial.

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REPLY: In their letter to the editor regarding our article titled "Metabolic Imaging of Infection" (*1*), Hess et al. disparaged our optimism for bacteria-targeted imaging and its potential for clinical application. They speculated based on mathematic permutations that "...bacterial concentrates in the body that are visible with bacterial PET tracers are more a rarity than a commonplace event."

Hess et al. submitted that the quantum of bacteria necessary to produce a detectable PET signal is not achievable in a human host. Although it is true that a higher bacteria load will produce a stronger PET signal, a lower bacterial load, much less than the 3.5×10^9 suggested by Hess et al., has been reported in different studies to produce detectable signal intensity. Pullambhatla et al. using ^{125}I-FIAU demonstrated detectable SPECT signal at a bacterial concentration of 1.4×10^9 CFU/mL (*2*), a level at which Hess et al. conjectured that PET signal will be barely detectable. Ordonez et al. reported a detectable PET signal with ^{18}F-FDS at a bacterial concentration of 1.1×10^6 CFU (*3*), 2 orders more sensitive than ^{18}F-FDG, which also detected the infection at this concentration (*4*). Bacterial load is not the only factor on which signal intensity is dependent. A high target-to-background ratio provides good contrast resolution. Weinstein et al. demonstrated an almost 1,000-fold-higher uptake of ^{18}F-FDS in bacteria than in mammalian cells (*5*). The minimum bacterial concentration Hess et al. estimated to be capable of producing a detectable signal was based on a PET volume resolution of 65 mm^3 and medium-sized bacteria volume of 4.2 μm^3. Their calculation failed to consider that in human infection the bacteria would be present together with immune cells and fibroblasts, easily making up that volume without having 3.5×10^9 CFU bacteria present.

The clinical utility of bacterial imaging with a radiolabeled antimicrobial peptide, ubiquicidine, has been shown (*1,6*). This is already a clear indication that bacterial-specific imaging is a reality and not a mirage.

Again, Hess et al. argued that in infection bacteria are scattered and instantaneously attacked and removed by the immune system, resulting in low numbers of bacteria. When bacteria are removed by the immune system the patient is likely to recover and would not require imaging. It is when the immune system is unable to curtail the infection with proliferating organisms that the patient would come to clinical notice; moreover, very high bacteria concentrations have been reported in human infections (*7*).

^{18}F-FDG remains the most commonly used PET tracer in clinical application. Its lack of specificity in differentiating sterile inflammation from infection, however, represents a significant limitation, especially in the postoperative period (*8*). An unmet need therefore remains in the clinical differentiation of inflammation from infection. Bacterial-specific imaging is a viable attempt to cater for this need, and efforts in this regard must be encouraged especially in view of the significant morbidity and mortality burden that infections continue to cause. Despite the prospects, there also remain challenges in the development of bacterial imaging including identifying probes that have sensitivity for a broader range of microbes rather than species-specific probes. This calls for more work to be done and not the pessimism expressed by Hess and colleagues.

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