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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 $3.5 \times 10^9$ 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 $1.4 \times 10^9$ 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 $1.1 \times 10^6$ 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 $\mu$m$^3$. 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 $3.5 \times 10^9$ 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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