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SUPPLEMENT ARTICLE

Visualizing Bacterial Infections With Novel Targeted Molecular Imaging Approaches

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Although nearly a century has elapsed since the discovery of penicillin, bacterial infections remain a major global threat. Global antibiotic use resulted in an astounding 42 billion doses of antibiotics administered in 2015 with 128 billion annual doses expected by 2030. This overuse of antibiotics has led to the selection of multidrug-resistant "super-bugs," resulting in increasing numbers of patients being susceptible to life-threatening infections with few available therapeutic options. New clinical tools are therefore urgently needed to identify bacterial infections and monitor response to antibiotics, thereby limiting overuse of antibiotics and improving overall health. Next-generation molecular imaging affords unique opportunities to target and identify bacterial infections, enabling spatial characterization as well as noninvasive, temporal monitoring of the natural course of the disease and response to therapy. These emerging noninvasive imaging approaches could overcome several limitations of current tools in infectious disease, such as the need for biological samples for testing with their associated sampling bias. Imaging of living bacteria can also reveal basic biological insights about their behavior in vivo.

Keywords. AMR; Enterobacterales; PET; pathogen-specific; *Staphylococcus aureus*.

Bacterial infections contribute significantly to the burden of infection-related deaths. A recent report estimates that 33 common bacterial pathogens were responsible for 7.7 million deaths worldwide in 2019 alone, comprising 13.6% of all global deaths and 56.2% of all sepsis-related deaths [1]. The 5 leading bacterial pathogens—*Staphylococcus aureus*, *Escherichia coli*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*—were responsible for 54.9% of deaths among the investigated bacteria [1]. Additionally, global antibiotic use was 42 billion doses in 2015 and is anticipated to be as high as 128 billion by 2030 [2], contributing to antimicrobial drug resistance. Importantly, antimicrobial drug-resistant infections are expected to become the leading cause of death worldwide by 2050, with an estimated 10 million deaths per year, exceeding the number of people dying from cancer [3].

Staphylococcus aureus is a major human pathogen that causes severe, deep-seated infections, including pneumonia, meningitis, brain abscesses, and implant-associated infections [4, 5]. The widespread prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) strains poses a major challenge for the treatment of these complicated infections. Similarly, the Enterobacterales order of rod-shaped gram-negative bacteria that inhabit the gastrointestinal tract represents the largest group of bacterial pathogens in humans and can produce a wide range of infections leading to sepsis and death. Among this group are *E coli*, *K pneumoniae*, *Enterobacter* spp, *Salmonella* spp, *Serratia* spp, and *Yersinia* spp, among others. The United States (US) Centers for Disease Control and Prevention has identified multidrug-resistant (MDR) strains of Enterobacterales such as extended-spectrum β-lactamase–producing and carbapenem-resistant Enterobacteriaceae as urgent threats to human health [6], which have become widespread globally. MDR infections due to Enterobacterales are associated with late diagnosis, a lower rate of appropriate empirical antibiotic treatment, and higher mortality [7]. Enterobacterales, especially *K pneumoniae*, are also a leading cause of secondary pneumonias in hospitalized patients, with coronavirus disease 2019 (COVID-19) [8]. A prominent Enterobacterales that causes plague—*Yersinia pestis*—is designated as a biothreat pathogen and was responsible for several past pandemics [9]. Finally, *Mycobacterium tuberculosis* remains one of the leading causes of death from a single infectious agent globally [10]. An estimated 10.6 million people fell ill with tuberculosis (TB) in 2021, an increase of 4.5% from the numbers in 2020 [10]. The COVID-19 pandemic continues to have a damaging impact on access to healthcare and reversing prior declines in the incidence of bacterial infections. The burden of drug-resistant TB (including MDR-TB strains

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resistant to the first-line TB drugs rifampin and isoniazid) also increased between 2020 and 2021, with 450 000 new cases of rifampin-resistant TB in 2021.

NEED FOR SPECIFIC DIAGNOSTIC IMAGING APPROACHES

When evaluating an infection at an inaccessible site, samples from blood, urine, stool, or cerebrospinal fluid are obtained but can be insensitive or unreliable for diagnosis, as the pathogens remain localized to the infectious lesion(s), without substantial systemic shedding. A systematic review showed that blood cultures from hospitalized patients with pneumonia were positive in only up to 14% of patients [11]. Invasive procedures, such as bronchoalveolar lavage or surgical resection and biopsy, are frequently used to rule out suspected conditions and establish a definitive diagnosis, but can be technically challenging with associated patient risk. Furthermore, the time required for invasive procedures can delay diagnosis, and tissue samples are generally only acquired from accessible lesions, at a single time point, potentially leading to sampling error. Therefore, noninvasive tools such as computed tomography (CT), magnetic resonance imaging (MRI), and nuclear medicine techniques such as radiolabeled white blood cell imaging imaged with single photon emission computed tomography and 2-deoxy-2-^{18}F-fluorodeoxyglucose (^{18}F-FDG) imaged with positron emission tomography (PET) are often incorporated into the diagnostic workup for these patients [12, 13]. However, these imaging tools lack specificity for infection, detecting morphological changes or host-immune responses to infection, and thereby cannot reliably differentiate infection from either malignancy or other causes of inflammation [14]. Moreover, host responses to infection may be impaired or absent in immunosuppressed patients (eg, cancer, chemotherapy, human immunodeficiency virus/AIDS, or organ transplant). This may make conventional imaging tests less sensitive to detecting infection in high-risk patients. Finally, current imaging approaches fail to provide rapid response monitoring or information on the adequacy of a selected antibiotic regimen. Therefore, there is an unmet clinical need for rapid, whole-body imaging that can specifically localize a pathogen, assist in image-guided body fluid sampling, provide a quantitative readout of disease burden, and indicate successful response to antibiotic therapy.

MECHANISM(S) OF BACTERIAL SPECIFICITY

Previous attempts at developing pathogen-specific imaging approaches have been based primarily upon radiolabeling existing antibiotics or antimicrobial peptides (reviewed in [15, 16]). Although these approaches are potentially more specific than existing clinical tools, as they necessarily must have a therapeutic window for efficacy in bacterial cells over mammalian cells, they may not be ideal imaging agents, unless there is a mechanism for bacterial accumulation of the tracer that is orders of magnitude greater than for the healthy adjacent tissues (Figure 1). This can be true for some, but not all antibiotic classes, but it is an essential characteristic for a successful pathogen-specific imaging agent. Additionally, radiolabeling efforts are often not straightforward, and several approaches have generated notable failures, for example, chelation-based radiochemical labeling that may negatively impact bacterial binding [17]. For example, ^{99m}Tc-ciprofloxacin was evaluated in a clinical study for diagnosing infections [18], but follow-up studies demonstrated nonspecific binding and an inability to differentiate infection from sterile inflammation [19]. Similarly, many antimicrobial peptides have been developed and tested in animal and human studies [15, 16], but none have been introduced into routine clinical care. Going forward, both preservation of the structure-activity relationship of the radioprobe to the target and conserved mechanisms for bacterial accumulation (engendering orders of magnitude greater binding to bacteria than for the healthy adjacent cells and tissues) need to be considered. Although bacteria-specific radiolabeled antibodies have also been studied in preclinical models with encouraging results [20], they may be limited in their ability to differentiate live compared to dead bacteria, and full-length antibody approaches have slow clearance from nontarget sites [21].

In contrast, divergent evolution has provided unique metabolic pathways in bacteria (prokaryotic) that are very different from mammalian (eukaryotic) cells, which can be utilized to develop bacteria-specific imaging approaches [22]. This strategy is akin to those used in clinical microbiology where selective metabolism of small molecules (especially sugars) has been used for several decades to differentiate microbes [23]. Substrates that exploit a mechanism for substantial bacterial accumulation such as using enzymatic turnover, or through multiple bacterial binding sites (eg, specific retention in the cell wall or other macromolecules), could allow bacterial visualization over the background host (mammalian) tissues [14]. Successful approaches are frequently based on small-molecule substrates that easily penetrate diseased tissues, are rapidly cleared from nontarget tissues, are stable due to covalently bonded or "trapped" radionuclides, and are generally cost-effective and simple to produce. Small molecules selectively metabolized by pathways expressed only in bacteria (or even in a specific class or species of bacteria) can not only be exploited to differentiate bacterial infections from noninfectious inflammatory processes accurately but can also provide information on the causative bacterial class or species [22]. While a systematic screen of approximately 1000 random, small molecules to identify potential candidates has been conducted previously [22], much larger screens incorporating tens to hundreds of thousands of small molecules of a chemically diverse

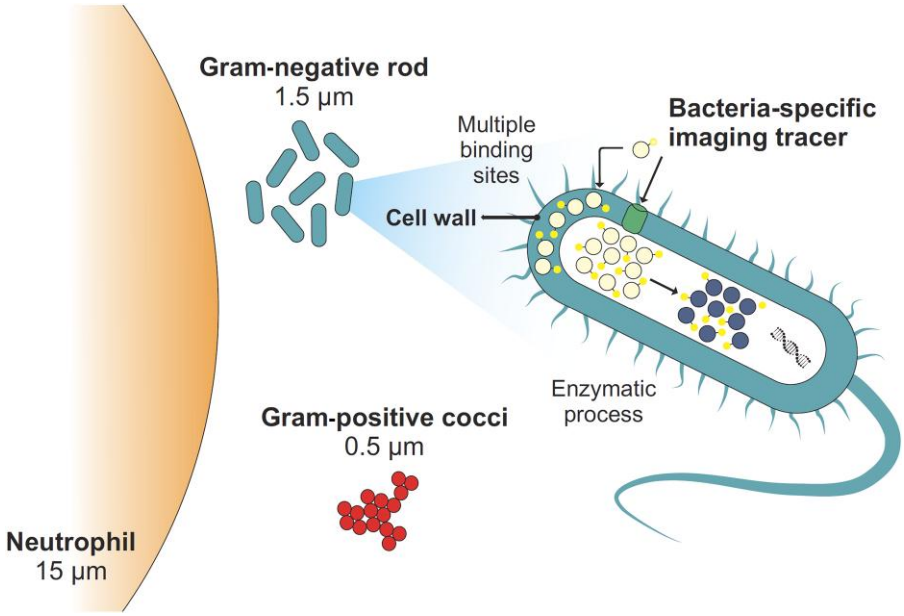

Figure 1. Development of bacteria-specific imaging tracers. Divergent evolution has provided unique metabolic pathways in bacteria (prokaryotic) that are very different from mammalian (eukaryotic) cells, which could be utilized to develop bacteria-specific imaging approaches. However, since bacteria (gram-negative rods and gram-positive cocci shown) are much smaller than the host cells (neutrophil shown), substrates that exploit a mechanism for substantial bacterial accumulation such as using an enzymatic process, or through multiple bacterial binding sites, are essential to allow bacterial visualization over the background host (mammalian) tissues. Adapted with permission from Ordonez et al [14]. ©2019 American Association for the Advancement of Science.

pool of compounds are needed. This could utilize current libraries used to develop antibiotics but with selection criteria different from those needed for selecting antibiotic candidates (killing the bacteria at the lowest possible concentration) but akin to those described by Ordonez et al [22] for selecting potential imaging candidates, which includes substantial bacterial accumulation, in addition to bacterial specificity. Some recently developed bacteria-specific metabolic imaging agents include ^{11}C-*para*-aminobenzoic acid (PABA) / 2-^{18}F-PABA and ^{11}C-trimethoprim (TMP), which target the bacterial folate pathway [24, 25]; ^{18}F-labeled maltohexaose and 6-^{18}F-fluoromaltotriose, which are taken up via the maltodextrin transporter in bacteria [26, 27]; radio-analogs of D-amino acids that are incorporated into the bacterial cell wall [28]; siderophore-derived agents [29]; and 2-^{18}F-fluorodeoxysorbitol (^{18}F-FDS) [14, 30, 31]. Some bacteria-specific imaging agents, such as PABA, which is metabolized via the bacterial folate pathway, are not affected by the bacterial growth phase [22]. However, other imaging agents requiring enzymatic activation based on adenosine triphosphate may have reduced sensitivity in infections where bacterial populations are predominantly metabolically slow or inactive. Fast enzyme kinetics are also required to rapidly catalyze bacterial trapping/accumulation of the imaging candidate before host metabolism/excretion of the tracer decreases the available probes below accumulation thresholds [32]. For example, some D-amino acids are enantioselectively recognized by certain flavoenzymes present in mammalian cells, which may reduce specificity and an opportunity for synthetic chemists to design radiolabeled amino acids with optimized pharmacokinetics and reduced mammalian metabolism [33].

Rigorous preclinical studies designed to mimic clinical infections are critical for the initial evaluation of any new imaging tracer, with a well-defined mechanistic basis (Table 1). In vitro assays are required to measure tracer uptake by both bacteria and control cells (heat-killed bacteria, mammalian cells) to establish specificity at a tracer concentration anticipated in infected tissues. Additionally, the duration of incubation for in vitro assays should reflect the physical half-life of the radioisotope (eg, 109 minutes for fluorine-18) as well as the biological half-life of the imaging molecule [30]. Uptake assays utilizing reference clinical bacterial strains, including MDR isolates, should be performed [22, 30, 34]. Animal models for bacterial infections have successfully replicated key features of human disease and have been used to develop many successful bacterial therapies [35, 36]. However, animal studies should take into consideration the bacterial burden at the infection site (which is generally high for acute infection: approximately 2×10^8 bacteria/mL in soft-tissue and peritoneal infections [37] and approximately 10^7–10^9 mycobacteria in cavitary TB lesions in humans [38]) and tissue penetration and pharmacokinetics of the tracer as well as appropriate confounding physiological and

Table 1. Development of Bacteria-Specific Imaging Tracers

Development Stage	
Discovery and preclinical development	
Tracer selection	Divergent evolution has provided unique metabolic pathways in bacteria (prokaryotic) that are vastly different from mammalian (eukaryotic) cells. • Screen large chemically diverse libraries to select molecules with potential bacterial specificity • Develop agents with well-defined mechanism(s) for bacterial metabolism and accumulation • Perform in vitro assays of PET tracers with appropriate controls to establish specificity • Test both reference and clinical strains including MDR isolates
Animal studies	Many infections have high bacterial burdens, which can be visualized using PET. • Perform dynamic imaging studies to establish in vivo pharmacokinetics and imaging strategy • Use controls (sterile inflammation and/or oncologic processes) within the same animal to establish specificity • Data must be normalized to the bacterial burden at the time of imaging, established ex vivo
Clinical development	
Patient selection	Due to the use of subpharmacological drug dosing utilized for PET studies, the safety profile is highly favorable, leading to a simpler pathway for the initial clinical studies compared to novel therapeutics. • Compare new imaging approaches with the "gold standard" (eg, direct sampling) • For the initial studies, select patients with known infection and minimal duration of antibiotic treatment • Enroll control subjects (sterile inflammation and/or oncologic processes) to establish specificity
Implementation	
Research	Currently, no routine clinical imaging technology is available for the specific detection or monitoring of bacterial infections. • Conduct cross-species animal and human studies that could validate animal models with human disease • Study microbial behavior in vivo, particularly in the context of biofilms and implant-related infections • Bacteria-specific tracers could stratify patients needing shorter or longer durations of antibiotic treatment
Clinical use	Host inflammation and tissue damage are variably present in patients with reduced immune responses and/or persist even after elimination of bacteria. Therefore, conventional imaging may be unreliable and cannot provide rapid assessments of therapeutic response to treatments. • Diagnosis of bacterial infection in patients with fever of unknown origin • Localization of infection in patients with known bacterial infection, but unknown sites(s) (occult infection) • Monitoring response to antibiotic treatments as well as detection of infection's nonresponse to antibiotics (drug-resistant bacteria, lack of antibiotic access) • Specificity for different classes of bacteria (gram-positive, gram-negative, mycobacteria) could be utilized to streamline empiric antibiotic treatments
Biases	Pragmatic approach is needed to overcome perception biases. • Educate patients and providers regarding radiation exposures • Cost of imaging is much lower in LMICs and access is higher than anticipated

Abbreviations: LMICs, low- and middle-income countries; MDR, multidrug-resistant; PET, positron emission tomography.

pathological processes—for example, metabolism, sterile inflammation, and vascular leakage, among other variables. Moreover, since the metabolic state of bacteria in situ is dependent on several factors, such as whether it is actively dividing or quiescent, development of imaging tracers (eg, PABA) that are not affected by the bacterial growth phase will be important primarily to target implant infections [22, 32], for which a sizable proportion of bacteria may be less metabolically active. Finally, since many bacteria divide rapidly (every 20–30 minutes), sensitivity of the imaging approach should be reported as the bacterial count at the time of imaging, and not what is injected into the tissues.

CLINICAL DEVELOPMENT OF LEAD TRACERS

Several bacteria-specific tracers have recently been tested in clinical studies [32, 34, 39, 40]. Due to the use of subpharmacological drug dosing utilized for PET studies (nanograms to micrograms of the drug injected per patient), the safety profile is highly favorable, leading to a simpler pathway for obtaining the required governance approvals for the initial clinical studies, if doses can be kept within the microdosing range (<100 μg of the drug injected per patient) [41]. However, the single greatest challenge is the recruitment of patients for initial validation studies due to the clinical practice of initiating empiric antibiotics for suspected infections before a definitive diagnosis has been established. This can lead to a variable residual bacterial burden and can affect the sensitivity of the imaging approaches being tested. Additionally, current clinical practice uses the presence of radiologically evaluable lesions (on CT, MRI, ultrasound, radiographs) as evidence of infection, which may be unreliable since infectious lesions predominantly comprise host-inflammatory cells and edema, and some may be sterile [42]. This contrasts with oncological imaging where there is a much higher percentage of cancer cells compared to host-immune cells in the lesion. Conversely, some bacterial infections may be present in a clinically silent form in tissues or organs outside of the primary infection site and thus be detected on whole-body imaging approaches. These issues are important for establishing a reliable measure

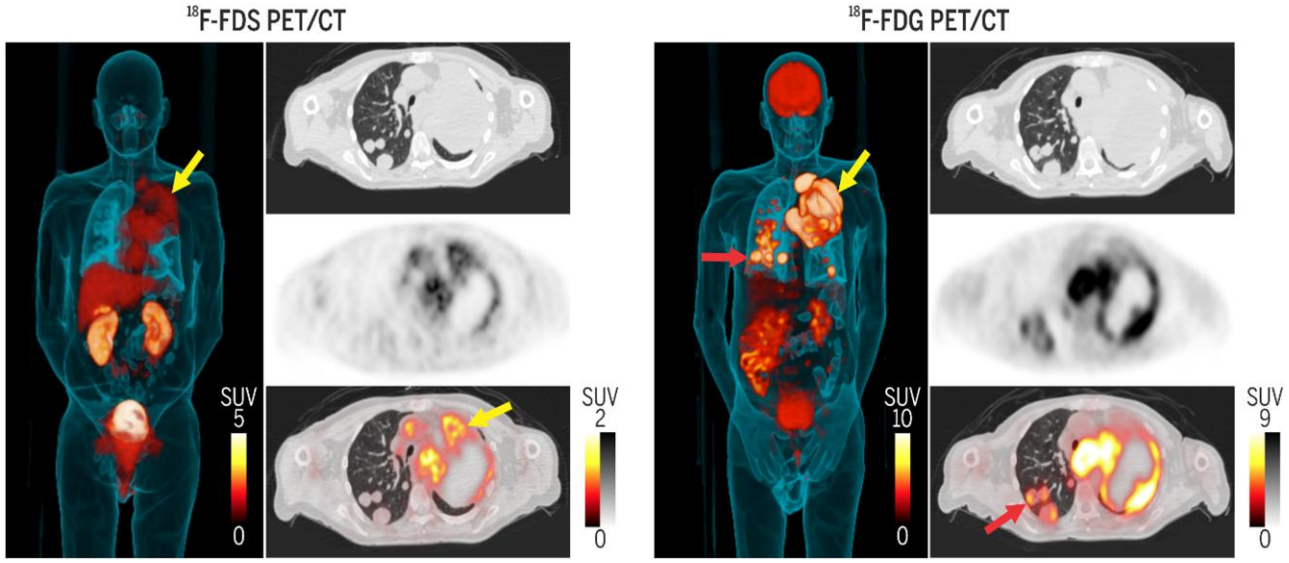

Figure 2. ^{18}F-Fluorodeoxysorbitol (^{18}F-FDS) positron emission tomography/computed tomography (PET/CT) imaging in a patient with coexisting cancer and infection. A patient with squamous cell carcinoma of the lung and *Klebsiella pneumoniae* pneumonia underwent ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET for clinical reasons 12 days after the study-related ^{18}F-fluorodeoxysorbitol (^{18}F-FDS) PET. Note the multiple ^{18}F-FDG-avid pulmonary tumors (red arrow, right panel). ^{18}F-FDG PET signal is also noted in the infected lesions (yellow arrows, right panel) and in the brain (right panel). However, the ^{18}F-FDS PET signal is only visualized in the infected tissues (yellow arrow). Reproduced with permission from Ordonez et al [34]. ©2021 American Association for the Advancement of Science.

for infection against which new imaging approaches should be tested, and the "gold standard" should be the detection of *live* bacteria directly within the infectious lesion(s) being evaluated, rather than the indirect detection of the sequelae of infection on morphological imaging (eg, CT, MRI) [34]. As this approach requires invasive tissue sampling, we understand that this "gold standard" is challenging to implement in clinical studies but should be sought. Other approaches could include the detection of infectious lesions on conventional imaging, with a high probability that they are the source of *live* bacteria in a relevant clinical sample. Control subjects without a bacterial infection, but other pathological processes such as cancer or inflammatory disorders, should also be included to demonstrate specificity (Figure 2). Finally, demonstration of changes in the imaging signal on repeat imaging in response to antibiotic treatment adds further support to the specificity of the technique [34]. Overall, there is a need for well-designed, prospective, multicenter clinical studies to develop new bacteria-specific imaging approaches, where patients are enrolled with a confirmed diagnosis, established using a reliable "gold standard," and preferably treatment naive or with minimal antibiotic treatments.

BARRIERS FOR CLINICAL USE

Generic imaging approaches that exploit universal processes or pathways that are specific to bacteria (eg, PABA, TMP, D-amino acids) have the potential to detect a wide range of pathogenic bacteria and have great clinical potential to diagnose and localize bacterial infection sites in patients with fever of unknown origin or those with an occult infection from a known organism but from an unknown site or sites and in special populations (eg, patients with cystic fibrosis) (Figure 3). Host inflammation and tissue damage can persist for long periods even after elimination of bacteria. Therefore, conventional imaging approaches using radiographs, CT, MRI, and ultrasound cannot rapidly assess therapeutic response to antibiotic treatments. However, repeat imaging utilizing bacteria-specific approaches can overcome this limitation and could also allow the detection of MDR organisms not responsive to treatment [30, 34]. Similarly, imaging approaches targeting a class of bacteria (eg, Enterobacterales for FDS) could be utilized to streamline empiric antibiotic treatments, which are highly dependent on the type of bacteria (gram-positive, gram-negative, mycobacteria). Finally, imaging provides spatial information, which could be useful to differentiate true infections from the normal human flora, for example, to distinguish normal gut microbiota in the lumen from extraluminal uptake as in abdominal or peritoneal infections. Of note, there is growing evidence that polyclonal bacterial populations with genetic diversity as well as different antimicrobial susceptibilities may coexist at infection sites [43, 44]. Given that the vast majority of metabolism-based bacterial-specific imaging tracers target highly conserved pathways, the polyclonal populations should continue to be detected using these approaches. However, this should be considered as one of the issues if initial clinical

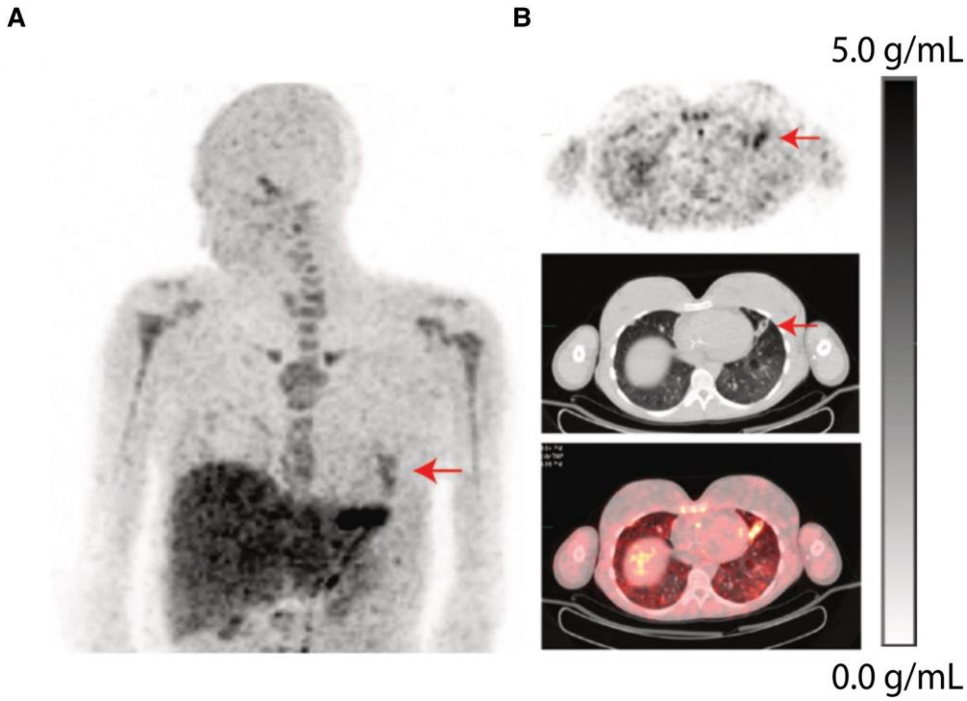

Figure 3. ^{11}C-Trimethoprim (^{11}C-TMP) positron emission tomography/computed tomography (PET/CT) in a patient with acute exacerbation of cystic fibrosis. *A*, ^{11}C-TMP PET/CT (325 MBq) images from a 21-year-old female with cystic fibrosis and a background of known multifocal opacities, who presented with symptoms of an acute exacerbation. The red arrow indicates the area of the identified bacterial lesion. Patient was on intravenous antibiotics at the time of imaging. *B*, Coronal and axial PET/CT images show a distinct lingular lesion with abnormal ^{11}C-TMP uptake, suggesting a site of superimposed pneumonia. Reproduced with permission from Lee et al [40]. ©2022 via CC BY 4.0 license.

studies demonstrate substantially inferior diagnostic accuracy compared to preclinical studies.

^{18}F-FDG PET has emerged as a highly sensitive approach for whole-body detection of a wide range of pathological processes such as cancer, inflammation, and infection. Importantly, ^{18}F-FDG PET is increasingly being incorporated into the diagnostic workup of patients with fever of unknown origin [45, 46]. However, ^{18}F-FDG PET is not universally reimbursed in all jurisdictions for the indications related to infections with the US being a notable example, which has limited its widespread use as well as incorporation into the clinical workflow. Therefore, PET is less available than other imaging technologies (CT, MRI), even in countries with a high percentage of gross domestic product expenditure on healthcare, and is generally limited to standard working hours with little or no availability out-of-hours. Given the high costs of PET and the required supporting infrastructure, there is a perception that these technologies are only viable in resource-rich settings, which contrasts with the disproportionate burden of infectious diseases in low- and middle-income countries (LMICs). However, several LMICs, where infections are still the leading cause of death and disability, have witnessed considerable growth in the installation and use of advanced imaging [47]. Additionally, the costs of imaging are substantially lower in LMICs than in the US and other high-income countries [48]. Several common PET isotopes are short-lived, with a half-life of a few hours, and therefore require a cyclotron in close proximity, which is expensive and also requires highly trained personnel. However, fluorine-18 (^{18}F)–based PET tracers (especially the widely available ^{18}F-FDG) can be transported usually within a 2- to 3-hour travel radius, and isotopes such as gallium-68 can be produced without the need of a cyclotron using a generator [49]. Highlighting the use of readily available ^{18}F precursors, ^{18}F-FDS, a bacteria-specific PET tracer currently in development, can be easily synthesized from ^{18}F-FDG without the need of any specialized equipment or personnel [50, 51].

Another barrier is the perceived risk of radiation exposure from imaging approaches such as PET or CT. However, technological advancements have substantially decreased the radiation exposures due to both PET and CT [22]. These developments include the proliferation of modern time-of-flight PET detectors [52], the use of PET–magnetic resonance in addition to PET-CT [39], and advances in total-body PET imaging allowing the generation of equivalent image quality with substantially lower injected radioactivity [53]. Even without total-body PET, the radiation burden from PET is low and generally at the level of annual background radiation

[54]. Importantly, unlike ^{18}F-FDG, which is retained by a diverse range of tissues, there is limited background uptake of most bacteria-specific imaging tracers by normal mammalian tissues. Therefore, these tracers are rapidly eliminated from the body, with much lower overall radiation exposure. Pertinently, the mortality risk for many patients with serious bacterial infections, including due to MDR bacteria, is markedly higher than the theoretical risks of radiation and is equivalent to the mortality risk due to common cancers, where PET and CT are widely used [22]. Hence, a practical approach is needed to overcome this perception bias and increase the adoption of these technologies in infectious diseases and pediatric populations [54].

MRI-BASED APPROACHES

MRI provides excellent tissue contrast and resolution for anatomic imaging and offers some advantages over radiopharmaceutical imaging (eg, PET), such as the range of contrast mechanisms that can be provided and the lack of radiation exposure or the need for short half-life cyclotron-produced isotopes. Additionally, MRI sequences such as diffusion-weighted imaging have been shown to differentiate pyogenic abscesses from other pathologies, based on the limited free motion of water molecules within abscesses [55]. However, this technique is largely based on cell density and is not specific for infections. Magnetic resonance spectroscopy (MRS) is a major strength of magnetic resonance approaches, allowing noninvasive and specific identification of molecules; MRS has been used to detect bacterial infections [56], and several case reports and series describing this approach to detect lipid peaks characteristic of *M tuberculosis* have been reported [57]. While this is promising, MRS is limited by low sensitivity (several orders of magnitude less sensitive compared to PET on a molar basis) and spatial/temporal resolution. Definitive preclinical and clinical studies are therefore required to validate MRS for the detection of infections. To improve sensitivity, approaches based on the detection of molecules with exchangeable protons, chemical exchange saturation transfer, have shown promising results in animal models [58, 59]. Because no contrast agent is required, such approaches have great translational potential for detecting and monitoring bacterial infections. Finally, emerging MRI-based strategies may hold potential in the future including utilizing the nonradioactive isotope carbon-13 with significant signal enhancement from hyperpolarization approaches to visualize bacteria-specific metabolism, for example, the rapid metabolism of hyperpolarized 2-^{13}C-pyruvate into 1-^{13}C-acetate in bacteria in vitro [60]. However, hyperpolarization techniques require expensive and complex hyperpolarization equipment on-site and are therefore difficult to implement.

CONCLUSIONS

Bacterial infections contribute significantly to the burden of infection-related deaths, making it necessary to develop rapid, whole-body imaging techniques that can specifically localize pathogens and quantitatively measure disease severity. Molecular imaging approaches have great potential for detecting infections but have not been as widely developed as in other fields such as oncology, cardiology, and neurology. As new agents are being developed, it is important to consider the challenges and opportunities specific for infections. A multidisciplinary approach involving microbiologists, molecular imaging scientists, infectious diseases physicians, nuclear medicine physicians, and radiologists, as well as increased and sustained support for basic and translational research, is needed to develop new molecular imaging approaches for bacterial infections of the future.

Notes

Author contributions. S. K. J. wrote the initial draft and all authors edited the manuscript. X. C. generated the figures.

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filed US patent US20180104365A1 assigned to the University of Pennsylvania on radiotracer derivatives of trimethoprim for medical imaging. M. A. S. holds equity in Vellum Biosciences, a corporate entity that is commercializing trimethoprim radiotracers. A. A. O. and S. K. J. are inventors for US patent US20150250906A1 on bacteria-specific labeled substrates as imaging biomarkers, and for pending patent United States Patent and Trademark Office number 63/071 755 on the solid-phase cartridge to formulate ready-to-use ^{18}F-FDS, filed by Johns Hopkins University. S. K. J. has received research grants from Novobiotic LLC, T3 Pharma, and Fujirebio Diagnostics, and is a scientific consultant for Novobiotic LLC. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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